Metals and Kidney Autoimmunity

Pierluigi E. Bigazzi

Department of Pathology, University of Connecticut School of Medicine, Farmington, Connecticut USA

The causes of autoimmune responses leading to human kidney pathology remain unknown. However, environmental agents such as microorganisms and/or xenobiotics are good candidates for that role. Metals, either present in the environment or administered for therapeutic reasons, are prototypical xenobiotics that cause decreases or enhancements of immune responses. In particular, exposure to gold and mercury may result in autoimmune responses to various self-antigens as well as autoimmune disease of the kidney and other tissues. Gold compounds, currently used in the treatment of patients with progressive polyarticular rheumatoid arthritis, can cause a nephrotic syndrome. Similarly, an immune-mediated membranous nephropathy frequently occurred when drugs containing mercury were commonly used. Recent epidemiologic studies have shown that occupational exposure to mercury does not usually result in autoimmunity. However, mercury induces antinuclear antibodies, sclerodermalike disease, lichen planus, or membranous nephropathy in some individuals. Laboratory investigations have confirmed that the administration of gold or mercury to experimental animals leads to autoimmune disease quite similar to that observed in human subjects exposed to these metals. In addition, studies of inbred mice and rats have revealed that a few strains are susceptible to the autoimmune effects of gold and mercury, whereas the majority of inbred strains are resistant. These findings have emphasized the importance of genetic (immunogenetic and pharmacogenetic) factors in the induction of metal-associated autoimmunity. *In vitro* and *in vivo* research of autoimmune disease caused by mercury and gold has already yielded valuable information and answered a number of important questions. At the same time it has raised new issues about possible immunostimulatory or immunosuppressive mechanisms of xenobiotic activity. Thus it is evident that investigations of metal-induced renal autoimmunity have the potential to produce new knowledge with relevance to autoimmune disease caused by xenobiotics in general as well as to idiopathic autoimmunity. *Key words*: autoimmunity, gold, kidney, mercury, metals. — *Environ Health Perspect* 107(suppl 5):753–765 (1999).
http://ehpnet1.niehs.nih.gov/docs/1999/suppl-5/753-765bigazzi/abstract.html

Clinical manifestations, pathology, and pathogenesis of kidney disease are complex and diverse. They are easier to understand when divided into separate clinicopathologic entities on the basis of the renal structures (glomerulus, tubules, interstitium, and blood vessels) that are the primary targets of injury (*1*). Great progress in our knowledge of kidney disease has also been achieved through clinical and experimental studies that have revealed some of the immunologic mechanisms involved in renal diseases. For the benefit of readers with little knowledge of kidney pathology, I will first summarize in a schematic fashion the major immune-mediated kidney disorders (Table 1).

Kidney disease can be the result of glomerular and/or tubulointerstitial injury due to one or more of the following basic tissue reactions.

Inflammation (influx of leukocytes) in the glomerulus. Inflammation (influx of leukocytes) in the glomerulus causes a nephritic (glomerulonephritic) syndrome with increased permeability to red cells (hematuria) as well as decreased glomerular filtration rate (leading to increased blood urea nitrogen and creatinine). The glomerulus is also more permeable to proteins, which results in mild to severe proteinuria. There are various types of glomerulonephritis. Acute endocapillary glomerulonephritis is characterized by abrupt onset of renal dysfunction with hematuria of glomerular origin. Glomerular hypercellularity, composed of inflammatory cells and proliferating mesangial and endothelial cells, is the most important pathologic lesion (*2*). The prototype of this condition is poststreptococcal glomerulonephritis, but it has also been observed in other infectious diseases and in some patients with systemic lupus erythematosus (SLE) (*3*). Crescentic glomerulonephritis, also called rapidly progressive glomerulonephritis, causes hematuria and a rapid, progressive decline in glomerular filtration rate (*4,5*). Its pathology is characterized by glomerular inflammation, necrosis, and proliferating glomerular epithelial cells with formation of crescents occupying Bowman's spaces (*6,7*). Its immunopathology is variable. Linear binding of IgG and C3 to glomerular capillary loops is observed in patients with Goodpasture's syndrome. Granular deposits of IgG and C3 in the glomeruli are noted in patients with SLE. Pauci-immune crescentic glomerulonephritis with a negative immunofluorescence (IF) pattern (i.e., without demonstrable renal binding of immunoglobulins and complement) is observed in patients with vasculitides and is usually associated with circulating antineutrophil cytoplasmic autoantibodies (*8*).

Thickening of glomerular basement membranes. Thickening of glomerular basement membranes (GBMs), another basic tissue reaction affecting glomerular filtration, causes the nephrotic syndrome characterized by increased glomerular permeability with massive leakage of albumin (proteinuria, more than 3.5 g/day), hypoalbuminemia, and edema (*9,10*). It occurs in a pure nephrotic form (bland urine sediment, i.e., only albumin and no red cells) in patients with minimal-change disease or membranous nephropathy. The histopathology of minimal change disease shows a paucity of glomerular changes by light microscopy (*11–13*). Similarly, there are no detectable immune deposits by immunofluorescence. However, electron microscopy reveals effacement of podocyte foot processes, swelling of endothelial cells, and occasionally small subendothelial deposits. The pathogenesis of this condition is uncertain, but immunologic mechanisms may be involved (*11,14*). Membranous nephropathy, also called membranous glomerulonephropathy or membranous glomerulonephritis, is characterized by thickening of glomerular capillary walls and absence of inflammatory cells. Granular deposits of immunoglobulins and subepithelial electron-opaque deposits are present in the GBM (*15–17*). In addition, thin argyrophilic projections (spikes) arise from the lamina densa of the GBM. A mixed nephrotic/nephritic form of the nephrotic syndrome (with active urine sediment, i.e., hematuria and proteinuria) occurs in patients with mesangiocapillary glomerulonephritis, also called membranoproliferative glomerulonephritis, (*18–21*). Various degrees of increases in mesangial cells and matrix, as well as thickening of the capillary walls, distinguish several histopathologic types of mesangiocapillary glomerulonephritis.

This article is based on a presentation at the Workshop on Linking Environmental Agents and Autoimmune Diseases held 1–3 September 1998 in Research Triangle Park, North Carolina.

Address correspondence to P.E. Bigazzi, Department of Pathology, University of Connecticut School of Medicine, MC 3105, 263 Farmington Ave., Farmington, CT 06030. Telephone: (860) 679-2618. Fax: (860) 679-2936. E-mail: faasen@sun.uchc.edu

The outstanding collaboration of L. Kosuda and D. Greiner is gratefully acknowledged. Our studies of xenobiotic-induced autoimmunity are supported by grant ES03230 from the U.S. Public Health Service.

Received 23 February 1999; accepted 2 August 1999.

Table 1. Summary of major immunologically mediated kidney diseases.

Disease	Major clinical signs of renal disease	Kidney histopathology	Kidney immunohistopathology
Poststreptococcal glomerulonephritis	Nephronal hematuria, mild to severe proteinuria, oliguria, and eventual renal failure over weeks to months	Acute inflammation (PMN), proliferation of mesangial and epithelial cells	Granular IgG and C3 (subepithelial) deposits in GBM
Crescentic glomerulonephritis	Nephronal hematuria, variable proteinuria, renal failure over weeks to months	Acute inflammation (PMN), necrosis, proliferation of mesangial and epithelial cells, crescents in ≥ 50% of glomeruli	Linear IgG deposits in GBM and TBM (anti-GBM antibody-mediated type) Granular IgG and C3 (subepithelial) deposits in GBM (immune complex-mediated type) No immune deposits (pauci-immune and ANCA-associated type)
Minimal change disease	Edema, proteinuria, hypoalbuminemia	Effacement of foot processes of epithelial cells	No immune deposits or small subendothelial deposits
Membranous glomerulopathy	Heavy proteinuria (> 0.5 g protein/24 hr), hypoalbuminemia, edema	Thickening of GBM, no inflammation	Granular IgG and C3 (subepithelial) deposits in GBM
Membranoproliferative (mesangiocapillary) glomerulonephritis	Proteinuria and hematuria	Proliferation of mesangial and epithelial cells, thickening of GBM, inflammation (PMN and monocytes)	Granular C3 and IgG (subendothelial, intramembranous, subepithelial) deposits in GBM
Lupus nephritis	Proteinuria, hematuria	Normal glomeruli (class I, < 5%); pure mesangial alterations (class II, 15%); focal proliferative glomerulonephritis (class III, 20%); diffuse proliferative glomerulonephritis (class IV, 50%); membranous glomerulonephritis (class V, 15%)	Mesangial immune deposits (class II, III, IV, V) Subendothelial immune deposits (class III, IV) Subepithelial immune deposits (class V, III, IV)
Acute interstitial nephritis	Sudden decrease in renal function, fever, hematuria	Interstitial edema, inflammation, tubular necrosis	Infiltrates with T cells and macrophages. Tubular immune deposits in some cases
Chronic tubulointerstitial nephropathy	Polyuria, nocturia, mild proteinuria	Chronic inflammation, interstitial fibrosis, tubular atrophy	Infiltrates with T cells and macrophages

Abbreviations: ANCA, anti-neutrophil cytoplasmic autoantibodies; GBM, glomerular basement membrane; PMN, polymorphonuclear leukocytes; TBM, tubular basement membrane.

Morphologic and clinical manifestations. Many of these morphologic and clinical manifestations, defined by the term lupus nephritis, are observed in patients with SLE (*22–24*). The latest World Health Organization classification of renal pathology in SLE encompasses several types of renal glomerular changes. Kidney glomeruli may appear normal by light microscopy but show small mesangial immune deposits and are identified as class I. More severe pathology comprises pure mesangial alterations (class II), focal proliferative glomerulonephritis (class III), diffuse proliferative glomerulonephritis (class IV), membranous glomerulonephritis (class V), and advanced sclerosing glomerulonephritis (class VI). Immune renal deposits containing IgG, IgM and C3 are detected in most patients with SLE, either in the mesangium (especially in class II kidneys) or at the subendothelial (classes III and IV) or subepithelial level (especially in class V).

Tubulointerstitial syndromes. Inflammation of tubules and interstitium with relative sparing of glomeruli causes acute or chronic tubulointerstitial syndromes with defects in tubular function (*25,26*). Acute tubulointerstitial nephritis is characterized by a sudden clinical onset, decrease in renal function, fever, and hematuria. There is renal interstitial edema, leukocytic infiltration, and focal tubular necrosis (*27*). Chronic tubulointerstitial nephritis is distinguished by polyuria, nocturia, and mild proteinuria. Its histopathology shows mononuclear cell infiltration and fibrosis of the renal interstitium as well as tubular atrophy. Both acute and chronic tubulointerstitial nephritis are caused by reactions to certain drugs, infections, and/or immune mechanisms (*25*). Either form can be observed in kidneys of some patients with SLE, where interstitial inflammation may be predominant over the glomerular lesions.

Immunologically mediated injury is a common pathogenesis of the kidney disorders summarized above (*28–32*). Renal damage can be caused by deposition of preformed immune complexes present in the circulation. It can also be due to *in situ* immune complex formation. This may occur when antibodies bind to exogenous or endogenous antigens planted within kidney structures. Alternatively, antibodies may react with intrinsic components of glomeruli and/or tubules. Finally, kidney lesions can result from the activity and products of polymorphonuclear leukocytes (PMNs), effector T cells, and macrophages. In many cases the damaging immune responses are of an autoimmune nature, as they are directed against self-antigens of the kidney or other host tissues (*33–36*). The causes initiating autoimmune responses leading to human kidney pathology remain unknown. However, environmental agents such as microorganisms and/or xenobiotics are good candidates for that role. The concept that bacteria and viruses may cause autoimmune disease has been accepted for a long time, even though the evidence available is relatively sparse (*37,38*). Less recognized is the possible role of xenobiotics as inducers of autoimmunity (*39*).

Xenobiotics are foreign substances of synthetic, natural, or biologic origin that can affect the immune system and cause either immunosuppression or allergic and autoimmune responses (*39–50*). Metals, either present in the environment or administered for therapeutic reasons, are prototypical xenobiotics and can cause decreases or enhancements of immune responses. However, their influence on the immune system does not necessarily imply that they can induce autoimmunity, as shown by a group of metals comprising arsenic, beryllium, iron, nickel, and vanadium that have recognized immunotoxic activity. To date, there are no well-documented reports that these metals cause autoimmune responses or autoimmune disease (Table 2). A second group of immunotoxic metals, including cadmium, chromium, copper, lead, platinum, and zinc, has only occasionally been associated with autoimmunity (Table 2). However, exposure to silver, lithium, gold, and mercury often results in autoimmune responses. Silver has immunotoxic effects on human lymphocytes and neutrophils (*72*), but to date we have found no reports of kidney autoimmunity in humans. The lack of human autoimmune disease

Table 2. Metals associated with autoimmune responses and autoimmune disease.

Metal[a]	Autoimmune responses(human and/or animal)	Human autoimmune disease	Animal autoimmune disease	References
Arsenic, beryllium, iron, nickel, vanadium	None reported to date	None reported to date	None reported to date	(*51–55*)
Cadmium	Autoantibodies to laminin 1 (?)	None reported to date	None reported to date	(*56–59*)
Chromium	ANA (?)	SLE-like syndrome, pemphigus (?)	None reported to date	(*60–62*)
Copper	Autoantibodies to red cells (?)	None reported to date	None reported to date	(*60, 63*)
Lead	IgM autoantibodies to neuroproteins (NF160 and MBP) (?), IgG autoantibodies to neuroproteins (NF-68 and GFAP) (?)	None reported to date	None reported to date	(*64,65*)
Platinum	ANA (?)	None reported to date	None reported to date	(*66,67*)
Zinc	None reported to date	Multiple sclerosis cluster (?)	None reported to date	(*55,68–71*)
Silver	Autoantibodies to fibrillarin	None reported to date	None reported to date	(*72–75*)
Lithium	Autoantibodies to thyroglobulin, autoantibodies to thyroid peroxidase, ANA, autoantibodies to gastric parietal cells	Autoimmune thyroid disease, SLE-like syndrome	Autoimmune thyroid disease	(*76–79*)
Gold	ANA, anti-Ro autoantibodies, antiplatelet autoantibodies, autoantibodies to laminin 1	Autoimmune kidney disease, autoimmune thrombocytopenia, SLE-like syndrome, pemphigus	Autoimmune kidney disease	(*80–86*)
Mercury	Autoantibodies to fibrillarin, autoantibodies to laminin 1, autoantibodies to DNA and other ANA, autoantibodies to thyroglobulin	Autoimmune kidney disease, lichen planus, sclerodermalike disease	Autoimmune kidney disease, GvH-like disease, arthritis, vasculitis	(*44,58,86–93*)

Abbreviations: ?, isolated reports to be confirmed by additional studies; ANA, antinuclear antibodies; GvH, graft-versus-host; SLE, systemic lupus erythematosus. [a]Listed in order of autoimmune potential.

resulting from exposure to silver may be explained by studies of mice treated with this metal that develop autoantibodies to nucleolar antigens but for reasons still unknown have no significant renal immune deposits or apparent renal pathology (*73–75*). Lithium facilitates preexisting autoimmune thyroid disease, but its association with the development of a nephrotic syndrome is still uncertain (*77,94,95*). Finally, gold and mercury can actually induce autoimmune disease of the kidney and other tissues (Table 2).

Because of their demonstrated pathogenetic potential, in the present review I will focus on the autoimmune effects of gold and mercury. Autoimmune disease caused by gold was first described in the 1950s and 1960s but lately has not attracted much research attention. Thus, we lack up-to-date knowledge of the mechanisms involved in the loss of tolerance to self-antigens following the therapeutic administration of gold compounds. Conversely, mercury-induced autoimmunity has been amply investigated in both humans and experimental animals. Recent studies using genetically modified mice have provided interesting data on the *in vivo* interactions between mercury and immune cells responsible for cytokine production. This information may apply to autoimmunity induced by xenobiotics in general and perhaps to idiopathic autoimmunity (*44*).

Gold-Induced Renal Autoimmunity

Gold has been recently described as "possibly the most ancient and ... one of the most modern agents in all of medicine's pharmacopoeia" (*96*). It has also become one of the most common allergens and in some countries is second only to nickel in the etiology of cutaneous hypersensitivity reactions (*97*). In spite of these immunotoxic effects, environmental or occupational exposure to gold does not seem to cause major renal pathology. Workers employed in gold mining and refining as well as goldsmiths and neighbors of gold shops in the Amazon are more likely to show evidence of mercury, not gold, contamination (*98*). However, a recent report of rapidly progressive interstitial lung fibrosis (Hamman-Rich syndrome) in a goldsmith has raised the possibility that occupational exposure to this metal may occasionally have pathologic consequences (*99*). This is suggested by the occurrence of interstitial lung fibrosis, possibly with an autoimmune pathogenesis, as a rare complication of treatment with gold compounds (*100*).

The medical literature contains numerous reports of human disease from therapy with gold salts, self-administration of folk remedies containing gold, or the ingestion of liquor containing this metal (*101–105*). Since the 1920s, gold compounds have been employed in the western world for the treatment of rheumatoid arthritis (RA). In North America, gold sodium thiomalate and gold sodium thioglucose are used primarily in patients with progressive polyarticular RA (*106*). Gold therapy is also recommended for selected patients with juvenile RA, psoriatic arthritis, or ankylosing spondilitis. The mechanisms underlying the therapeutic effects of gold compounds are still rather uncertain, but recently it has been suggested that they inhibit the proinflammatory transcription factors AP-1 and NF-κB (*107–109*).

Both autoimmune responses and disease are well-documented consequences of gold treatment, as shown by numerous reports published in the period between 1960 and 1970 (Table 2). Unfortunately, little attention is currently given in the United States to gold-induced autoimmunity, and only a few European investigators have continued to study the pathogenesis of these adverse effects (*48,84,110*).

Effects of Gold on Cells of the Immune System

The literature on the immunotoxic effects of gold compounds is rather sparse. Early studies observed a gold-induced modulation of metabolic events in leukocytes (PMNs, B cells) stimulated by phorbol esters (*111,112*). Gold-containing compounds can inhibit mitogen-induced T cell activation and cause a marked decrease in interleukin (IL)-2 release by peptide-specific murine $CD4^+$ T-cell clones (*113*). Gold-induced inhibition of peptide recognition may be due to the formation of chelates between Au(I) and cysteine thiol groups of antigenic peptides. Such a process might contribute to the therapeutic effects of gold compounds in RA. Griem et al. (*110*), Goebel et al. (*114*), and Griem and Gleichmann (*115*) have also observed that mononuclear phagocytes exposed to Au(I) *in vitro* are capable of generating the reactive metabolite Au(III), which could explain the various immune reactions induced by gold-containing compounds.

Gold-Induced Human Autoimmunity

RA patients treated with gold may develop autoimmune responses to nuclear antigens and platelets. A recent report has shown that RA patients with gold-induced side effects produce antinuclear antibodies against the Ro antigen (*80*). When the sera of 29 RA patients positive for antinuclear antibodies were tested by Western blot using recombinant antigens (Ro 60 kD, Ro 52 kD, and La), one group of 13 reacted only with Ro 52 kD, another group of 10 reacted only with Ro 60 kD, and a third group reacted with all three antigens. The first group had severe skin eruptions, the second group had either proteinuria and/or leukopenia, and the third group had Sjögren's syndrome (*80*). Thrombocytopenia has also been observed in 1–3% of patients treated with gold salts (*81,116,117*). An association with HLA-DR3 and the presence of autoantibodies against platelet epitopes suggest the importance of immunologic mechanisms: platelet destruction may be mediated by these autoantibodies, either acting alone or in combination with gold (*81,118*).

Numerous reports of gold therapy followed by renal lesions can be found in the literature of the 1960s and 1970s (*85,119–121*). Proteinuria was detected in 6–17% and a nephrotic syndrome in 2.6–5.3% of RA patients treated with gold salts (*86*). The relative risk of proteinuria during gold treatment of RA was increased 32 times in patients who were HLA-DR3 positive (*122–125*). A survey of 122 RA patients who underwent kidney biopsy after the development of proteinuria showed that 41% of these subjects presented with a nephrotic syndrome. Membranous glomerulonephropathy was present in 89.5% and minimal change nephropathy in 9.6% (*86,126,127*). Such adverse effects of gold therapy are still occurring, as shown by a recent report of a patient affected by psoriatic arthritis who after 3 years of oral gold therapy developed membranous glomerulonephropathy, autoantibodies to myeloperoxidase, and vasculitis (*128*). It should be noted that there are close similarities between gold and penicillamine nephropathy (*127*). Finally, in view of the recent popularity of food supplements and folk medicines, often imported from overseas without a controlled designation of their composition, it is of interest that an oral tonic containing gold (known as Gold Kushta) has been associated with a nephrotic syndrome in some subjects (*101*) and that lichenoid dermatitis has been diagnosed in three patients who had consumed an alcoholic beverage containing gold (*105*).

Autoimmunity Induced by Gold in Experimental Animals

Early studies performed in outbred Wistar rats showed that injection of sodium aurothiomalate (0.025 mg once a week) caused proteinuria after 7 weeks of treatment (*129*). Kidney histopathology and immunohistopathology revealed diffuse thickening of glomerular capillary walls as well as granular glomerular deposition of rat immunoglobulins and complement. Electron microscopy showed electron-opaque deposits along the epithelial aspect of the renal GBM and loss of epithelial foot processes. Gold was detected only in proximal convoluted tubules. Rabbits fed flour containing an indigenous preparation of gold oxide (Gold Kushta) or injected with sodium aurothiomalate developed proteinuria as well as thickening of glomerular basement membranes and electron-opaque deposits (*101*). Similar effects followed the subcutaneous administration of sodium aurothiomalate to guinea pigs, with proteinuria, renal lesions, and immune complex nephropathy (*130*). Light microscopy revealed two different histopathology patterns. The first, characterized by interstitial mononuclear cell infiltration, tubular destruction, and interstitial fibrosis, was associated with the production of autoantibodies to tubular basement membranes. The second consisted of thickening of glomerular capillary walls and mesangial cellularity. It was associated with the production of autoantibodies to renal epithelial antigens and the glomerular deposition of granular immune complexes containing renal antigens and their specific autoantibodies.

These initial studies, performed in outbred animals and lacking the more sophisticated reagents and methods currently available, are still of some value because they demonstrate that different animal species are susceptible to gold-induced autoimmune effects similar to those experienced by humans. More recent studies have provided additional details on the pathogenesis of renal autoimmune disease caused by exposure to gold. Inbred mice of the A.SW strain (H-2^s) treated with gold sodium thiomalate produce autoantibodies to nucleolar antigens (*131,132*). Because the immunofluorescence pattern produced by these autoantibodies is similar to that observed in H-2^s mice injected with mercury, it is likely that the autoantigen involved is fibrillarin (see "Mercury-Induced Renal Autoimmunity"). Mice of this strain develop elevated levels of serum IgE, IgG, and IgM after 8 weeks of gold treatment (*133*). The oxidation state of gold, i.e., Au(III) versus Au(I), seems to play a major role in the immunotoxicity of this metal and its induction of autoimmune responses (*132*).

Brown Norway (BN) rats treated with gold salts develop autoimmunity (*83,84*). Autoantibodies reacting with the renal GBM, and in particular with laminin 1 (a component of the extracellular matrix), were found in all animals injected with aurothiopropanolsulfanate (*84*). Other autoantibodies (against nuclear antigens, double-stranded DNA, thyroglobulin, actin, myosin, and tubulin) were detected in gold-treated BN rats. In addition, serum IgE levels increased and showed a first peak at the end of the first week of gold treatment and a second, higher peak at the end of the third week. After 4 weeks, intense linear IgG deposits were present along the GBM and tubular basement membrane (TBM). Indirect immunofluorescence showed that eluates from these deposits reacted *in vitro* with GBM and TBM. Glomerular linear and/or granular deposits were also observed after 8 weeks of gold treatment. Light microscopy and electron microscopy showed that kidneys were normal after 4 weeks. Diffuse interstitial mononuclear cell infiltrates and small electron-opaque mesangial and subepithelial deposits were present after 8 weeks in some rats. The authors concluded that gold treatment of BN rats results in an autoimmune membranous glomerulopathy similar to that caused by mercury and penicillamine (*84*). The autoimmune effects of different gold compounds, including some thiol-containing salts, were also examined in BN rats (*83*). Sulfur-containing groups do not induce autoimmune responses but may potentiate the autoimmune effects of gold. The BN rat model has been recently pursued for studies of the cytokine network; both gold and D-penicillamine were found to upregulate the expression of mRNA for rat IL-4 (*134*).

Mercury-Induced Renal Autoimmunity

Mercury is a xenobiotic widely present in the environment. Its levels are increasing as a consequence of the processing of raw ores, various industrial activities, and the discharge of medical and scientific waste (*44,98*). One of the major routes of human exposure to mercury may currently be the ingestion of contaminated food, especially fish (*135*). The potential health risks of mercury released from dental amalgam fillings are still a source of controversy (*74,136,137*). Finally, a possible new source of mercury exposure may be unregulated dietary supplements and health remedies that contain other metals such as silver and gold (*101,138*). Both inorganic and organic forms of mercury have immunotoxic effects; suppression or potentiation of cellular immunity and antibody responses have been observed *in vitro* and *in vivo*. There is also solid evidence that mercury can induce autoimmunity both in humans and experimental animals (Table 2).

Effects of Mercury on Cells of the Immune System

The various cellular components of the immune system can be activated or inhibited by low levels of mercury (Table 3) (*44, 49,139–141*). A monocyte-dependent inhibition of phytohemagglutinin (PHA)- and phorbol-12-myristate-13-acetate (PMA)-induced

proliferation and decreased production of IL-2 has been observed in human T cells treated *in vitro* with $HgCl_2$. *In vivo* exposure to mercury increases T-lymphocyte responses in BALB/c mice and decreases them in Swiss and (B6 × C3)F_1 hybrid mice. Mercury also causes both apoptosis and necrosis of various T-cell lines (*142,143*). Spleen cell cultures from $HgCl_2$-treated BN rats exhibit a marked decrease in the concanavalin A-induced generation of interferon (IFN)-γ–producing cells, an inhibition likely caused by nitric oxide (*144,145*).

Early studies showed that human B cells treated with $HgCl_2$ and pokeweed mitogen were stimulated to produce IgE (*150*). However, more recent investigations have demonstrated that exposure to $HgCl_2$ *in vitro* may result in a dose-dependent inhibition of human B-cell proliferation and immunoglobulin yield (*163*). Similarly, murine B cells treated *in vitro* with mercury exhibit inhibition of both RNA and DNA synthesis and significant decreases in production of immunoglobulin isotypes (*152*). On the other hand, B lymphocytes from mercury-treated rats and mice are stimulated to produce IgE and other immunoglobulin isotypes (*149,151,153,154*). Investigations of mercury effects on macrophages have detected inhibition of phagocytosis and free radical production. Depending on its *in vitro* concentration, $HgCl_2$ stimulates H_2O_2 release from Lewis (LEW) but not BN macrophages and can inhibit phagocytosis in both LEW and BN resident peritoneal macrophages (*155*). Finally, treatment with $HgCl_2$ induces IL-1 production by murine macrophages (*156*) and higher gene expression of IL-12 in spleen cells of LEW rats (*164*). Studies of the effects of mercury on human PMN are quite sparse. Concentrations of $HgCl_2$ between 1 μM and 0.01 fM inhibited adherence, polarization, chemotaxis, and erythrophagocytosis of human PMN (*157*). In addition, 1 nM to 1 fM $HgCl_2$ significantly stimulated H_2O_2 production and chemiluminescence of these cells. Inhibition of microbicidal activities and respiratory burst, decreased superoxide anion formation, and chemotaxis have also been detected after exposure to methyl mercury, mercuric chloride, and silver lactate (*158,165,166*). To date, there are few investigations of other types of immune cells. BN rat peritoneal mast cells exposed to $HgCl_2$ have higher sensitivity to degranulation by a monoclonal antibody to IgE (*159*). Finally, treatment of mice or rats with methyl mercury causes reduction or suppression of natural killer cell activity (*141,162*).

Mercury-Induced Human Autoimmunity

At the present time mercury is not a frequent cause of human autoimmune disease. This may be a consequence of its progressively diminished use in medicine since mid-century, following the introduction of powerful nonmercurial diuretics and antiseptics. When drugs containing mercury were commonly used, they often caused autoimmune disease (Table 4).

Several instances of mercury-associated nephrotic syndrome after treatment with organomercurial diuretics for congestive heart failure, ingestion of mercury-containing laxatives, or the protracted use of ammoniated mercury in skin ointments for the treatment of psoriasis have been reported in the literature (*86*). A nephrotic syndrome associated with the use of skin-lightening creams containing mercury was also observed in numerous East African patients (*87,89*). Direct immunofluorescence showed that IgG and complement were bound at the level of the renal GBM in kidney biopsies from these patients. The nephrotic syndrome resulting from treatment with mercury was due to renal histopathologic lesions defined as membranous glomerulonephritis, membranous nephropathy, or membranous glomerulonephropathy (*15–17*). The lack of inflammatory changes at the glomerular level suggests that the two latter terms may be more appropriate. As noted in a recent textbook of general pathology, "the suffix -itis usually means inflammation of that organ or tissue (appendic-itis, mening-itis, pleur-itis)" (*168*). The presence of glomerular immune deposits cannot be considered equivalent to an ongoing inflammatory process, as antibody-mediated damage may occur without the presence of neutrophils, lymphocytes, and/or macrophages in the target tissues (*29,169,170*).

Occupational exposure to mercury does not usually result in autoimmune responses and disease (*58,59*). Early reports that workers in mercury-producing industry developed circulating antilaminin antibodies have not been confirmed (*58,171–173*). However, one cohort of workers exposed to mercury had a slight increase in autoantibodies to DNA (*58*). This observation may be of some interest, a few subjects with industrial exposure to mercury have also developed antinuclear antibodies, sclerodermalike disease, lichen planus, or membranous nephropathy (*91,92,167*).

Thus, when one examines the relevant literature, it is evident that mercury can cause autoimmune responses and disease in humans (Table 4), even if changes in therapeutics have obviously led to a decrease of these effects. However, the risk of autoimmune consequences continues to be present because mercury is currently used as a preservative in some immunoglobulin and vaccine preparations, and may be a contaminant of fish (*135*), imported food supplements, and unregulated health remedies. An additional but still controversial source of very low levels of mercury is provided by dental amalgam (*74,136,137,174*). Clearly, it is quite difficult to study in human subjects the autoimmune effects of the chronic exposure to very low levels of mercury, either alone or in association with other xenobiotics. These difficulties are not encountered when using experimentally induced models of autoimmune disease that provide the opportunity (otherwise impossible in clinical investigations) to initiate the exposure of laboratory animals to different doses of xenobiotics and ascertain their pathogenetic potential. Such investigations have provided excellent evidence that administration of mercury causes autoimmunity in rabbits, rats, and mice.

Mercury-Induced Autoimmunity in New Zealand White Rabbits

Mercury treatment of outbred New Zealand White (NZW) rabbits resulted in the formation of immune deposits in kidneys and other

Table 3. Effects of mercury on the immune system.

Cells of the immune system	Effects of mercury	References
T lymphocytes	↑ ↓ (↑ or ↓ IFN-γ,↑ IL-4)	(*144,146–148*)
B lymphocytes	↑ ↓	(*149–154*)
Macrophages	↑ ↓ (phagocytosis, free radicals, IL-1)	(*141,155,156*)
Polymorphonuclear leukocytes	↑ ↓ (chemotaxis, phagocytosis, free radicals)	(*157,158*)
Mast cells	↑ ↓ (degranulation, IL-8, TNF-α, IL-4)	(*159,160*)
Natural killer cells	↓ (killer activity)	(*161,162*)
Other cells	?	(*44*)

Abbreviations: ↑, increase; ↓, decrease; ?, unknown; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

Table 4. Mercury-induced human autoimmunity.

Source of mercury exposure	Autoimmune responses and immunopathology	Autoimmune disease	References
Diuretics	Immune deposits in renal GBM	Nephrotic syndrome	(*86*)
Laxatives	Linear and/or granular IgG and C3 at GBM	Nephrotic syndrome	(*86*)
Skin ointments	Linear and/or granular IgG and C3 at GBM	Nephrotic syndrome	(*87–89*)
Occupational or accidental	Autoantibodies to laminin 1 (?), ANA, autoantibodies to DNA Linear and/or granular IgG and C3 at GBM	Autoimmune kidney disease, lichen planus, sclerodermalike disease	(*58,90–92,167*)

Abbreviations: ?, reported, but not confirmed; ANA, antinuclear antibodies; GBM, glomerular basement membrane.

organs with two-stage kinetics (Table 5) (*175*). In the first stage, linear deposits of rabbit IgG (but not C3) were present in renal GBM and TBM. The immunoglobulins eluted from these deposits reacted with still unidentified autoantigens of the extracellular matrix. At this time, the histology of the kidney did not show abnormalities and there was only slight proteinuria. The second stage was observed after 5–7 weeks of $HgCl_2$ treatment and was characterized by granular deposits of IgG and C3 in GBM and TBM. Immunoglobulins eluted from these deposits reacted with components of the extracellular matrix. In this stage, light microscopy revealed thickening of the glomerular capillary walls in 60% of the rabbits. Electron microscopy identified focal electron-opaque subepithelial deposits. In summary, outbred rabbits injected with mercury experienced autoimmune responses to epitopes of the extracellular matrix. The kidney glomerulus was the major target, with *in situ* formation of immune complexes that caused morphologic and functional damage suggestive of a membranous nephropathy.

It is unfortunate that this model has not been used for additional in-depth investigations of the autoantigens involved. Dose–response studies would also be useful. Nonetheless, the available evidence demonstrates that a certain percentage of outbred animals are susceptible to the autoimmune effects of mercury and may actually develop an immune complex-mediated nephrotic syndrome after exposure to this metal.

Mouse Models of Mercury-Induced Autoimmunity

The mouse, currently the preferred animal for immunology studies, has been very useful in the investigation of mercury-induced autoimmunity (Table 6). Mice of various inbred strains (A/J, A.SW, B10.S and SJL/J) or outbred ICR mice treated with $HgCl_2$ develop antinucleolar and antinuclear autoantibodies (*49,176,178–180,182–185*). The antinucleolar autoantibodies react with fibrillarin (U3 RNP protein) and occasionally with other nucleolar proteins of 60–70 and 10–15 kDa. This reaction is similar to that observed with autoantibodies from a subset of patients with scleroderma (*180,186*). Autoantibodies to fibrillarin belong to all IgG subclasses, with a predominance of IgG1 and IgG2a isotypes. They are detected after 3–5 weeks of mercury treatment and can be found in the circulation for 10–12 weeks and up to at least 1 year after discontinuation of mercury treatment. Dose–response studies have shown that autoantibodies to fibrillarin develop in mice treated with at least 1.225 ppm $HgCl_2$ in their drinking water for 10 weeks, a dose resulting in a mercury body burden similar to that observed in some occupationally exposed human subjects (*183*). A smaller percentage of mercury-treated mice produce autoantibodies to epitopes of nuclear antigens (chromatin and/or histones). The autoimmune effects of mercury in mice are in large part determined by the MHC, but background non-MHC genes may also be involved, as occurs in rats (*187,188*).

The kidneys of mercury-treated inbred (SJL, ASW, BALB/c) and outbred ICR mice contain granular immune deposits, mostly localized in the glomerular mesangium and the walls of interlobular arterioles and arteries (*178*). Interestingly, mice of the A.CA/SnJ, DBA/1J, and P/J strains that also produce antifibrillarin autoantibodies do not show renal immune deposits, for reasons that are still unclear (*181*). Immune deposits present in kidneys of SJL mice comprise IgG (containing autoantibodies to fibrillarin) and C3. Kidney histopathology is minimal and does not show serious inflammatory damage. It is characterized by widening of glomerular mesangial areas, electron-opaque deposits, and a moderate increase of endocapillary cells. The preferential involvement of the mesangium suggests the term mesangial glomerulonephropathy. In conclusion, the pathogenesis of mercury-induced kidney autoimmune disease in mice may be due to deposition of immune complexes and activation of the complement system. The lack of detectable inflammatory cells raises doubts about a pathogenetic role of effector neutrophils, lymphocytes, and macrophages.

Rat Models of Mercury-Induced Autoimmunity

The first rat model for immunopathologic investigations of autoimmunity caused by mercury was established in outbred Wistar rats injected subcutaneously three times a week with $HgCl_2$ (*189*). Approximately 33% of these rats developed significant proteinuria and a membranous glomerulonephropathy, with diffuse thickening of glomerular capillary walls and granular subepithelial deposits of immunoglobulins and complement. A similar model, but with a much higher incidence of autoimmunity, was later developed in inbred rats (*190,191*). Up to 100% of mercury-treated BN, MAXX, and Dorus Zadel Black (DZB) rats produce autoantibodies to antigens of the renal GBM, in particular laminin 1 (Table 7). The concentration of these autoantibodies in the serum increases 9–10 days after the start of mercury treatment and usually reaches a peak after 14–15 days. Circulating autoantibodies to laminin 1 decrease after 16–18 days and eventually return to baseline levels in the following days. The isotypes of these autoantibodies are usually IgG1 and IgG2a (*201,202*). As shown in Figure 1, IgG1 and IgG2a autoantibodies to laminin 1 increase significantly on day 11 of mercury treatment, but only those of the IgG1 isotype are still significantly elevated on day 15. Interestingly, binding of rat complement by these autoantibodies has not been detected either *in vivo* or *in vitro* (*192,203*). After BN rats have recovered from mercury-induced autoimmunity, they no longer develop autoimmune responses following further treatment with this metal. Serum autoantibodies against laminin 1 are also present in untreated BB rats with insulin-dependent diabetes mellitus and exposure to mercury increases both autoantibody levels and percentage of rats with circulating laminin antibodies (*197*). Rats of the PVG strain develop autoantibodies to nuclear antigens

Table 5. Kidney autoimmunity induced by $HgCl_2$ in New Zealand White rabbits.

Stage	Autoimmune responses	Kidney immunopathology	Kidney histopathology	Reference
First stage (2–3 weeks of $HgCl_2$ injections)	Autoantibodies to extracellular matrix (laminin 1 ?)	Linear deposits of IgG and C3 in GBM and TBM	Normal appearance of GBM and TBM	(*175*)
Second stage (5–7 weeks of $HgCl_2$ injections)	Autoantibodies to extracellular matrix (laminin 1 ?)	Granular deposits of IgG and C3 in GBM and TBM	Subepithelial immune deposits (membranous nephropathy after 8–12 weeks)	(*175*)

Abbreviations: ?, still unidentified; GBM, glomerular basement membrane; TBM, tubular basement membrane.

Table 6. Mouse models of kidney autoimmunity induced by $HgCl_2$.

Inbred strain	Autoimmune responses	Kidney immuno-pathology	Kidney histopathology	Duration of autoimmunity	References
SJL/J A/J A.SW B10.S	Autoantibodies to fibrillarin (and auto-antibodies to histones)	Granular deposits of IgG and C3 in renal mesangium	Mesangial glomerulopathy	At least 1 year	(*131, 176–180*)
A.CA/SnJ, DBA/1J, P/J	Autoantibodies to fibrillarin (and auto-antibodies to histones)	None detected	None detected	Not reported	(*181*)

Table 7. Rat models of kidney autoimmunity induced by $HgCl_2$.

Rat strain	Autoimmune responses	Kidney immunopathology	Kidney histopathology	Duration of autoimmunity	References
Outbred Wistar	Not reported	Linear/granular deposits of IgG in GBM and TBM	Membranous glomerulonephropathy	Not reported	(*189*)
Inbred BN and MAXX	Autoantibodies to laminin 1 (autoantibodies to thyroglobulin, myeloperoxidase, DNA)	Linear/granular deposits of IgG in GBM and TBM	Membranous glomerulonephropathy	≈ 30 days	(*190–193*)
Inbred DZB	Autoantibodies to laminin 1	Faint linear and strong granular deposits of IgG and C3 in GBM and TBM	Membranous glomerulonephropathy	Not reported	(*194*)
Inbred PVG	Antinuclear antibodies (antihistones)	Granular deposits of IgG and C3 in GBM and TBM	Membranous glomerulonephropathy	Not reported	(*195,196*)
Inbred BB (DP)	Autoantibodies to laminin 1, thyroglobulin	No IgG deposits	None induced by $HgCl_2$	Not reported	(*197*)
Inbred LEW	Suppression	No IgG deposits	None induced by $HgCl_2$	Not reported	(*198–200*)

Abbreviations: BN, Brown Norway; DP, diabetes prone; DZB, Dorus Zadel black; GBM, glomerular basement membrane; LEW, Lewis rats; TBM, tubular basement membrane.

after mercury treatment. To date no antibodies to laminin 1 or other autoantibodies have been detected in these animals. Finally, rats from the LEW and several other inbred strains are resistant to the autoimmune effects of mercury (*191,204*).

Autoantibodies to DNA, thyroglobulin, type IV collagen, heparan sulfate proteoglycan, entactin, etc., have also been detected in BN rats after exposure to mercury. However, they are usually present at low levels for brief periods of time and do not seem to cause disease of the kidney, thyroid, or other organs. Conversely, mercury-treated BN, MAXX, and DZB rats have renal immune deposits containing autoantibodies to laminin 1. The kinetics of immune complex deposition are similar to those observed in $HgCl_2$-injected outbred rabbits but with an accelerated course. The first stage, identified by linear deposits of IgG (mostly IgG1 and IgG2a) in GBM and TBM, reaches a maximum on approximately the 15th day of treatment. Eluates from these deposits contain autoantibodies to laminin 1, whereas C3 is usually undetectable. Linear deposits of IgG (likely containing the same autoantibodies) are present in basement membranes of spleen, liver, adrenals, and heart (*44,205*). Similar linear deposits of IgG are also found in basement membranes of the intestine after oral administration or subcutaneous injection of $HgCl_2$ (*44,206*). The second stage of immune deposition is observed after 15–20 days of mercury treatment and is characterized by granular IgG at the level of renal GBM and TBM. Autoantibodies to laminin 1 are also detected in eluates from these deposits. The renal immunopathology of $HgCl_2$-injected DZB rats is slightly different because after 6–10 days of treatment there is only a faint linear IgG deposition along the GBM. Abundant granular IgG deposits become evident at a later time. Mercury-treated PVG rats experience only granular IgG deposits in the GBM, without an initial linear stage. It is also of interest that $HgCl_2$-injected BB rats with circulating autoantibodies to laminin 1 have no immunoglobulin deposits either in the GBM or other tissues.

The clinical signs induced by mercury in BN and MAXX rats are reminiscent of the human nephrotic syndrome. Peak levels of proteinuria are usually detected after 14–16 days of mercury treatment, with high levels still present after 32 days (*192*). Autoantibodies against laminin 1, present in the circulation of mercury-treated BN, MAXX, and DZB rats, may have a pathogenic role, as demonstrated by their correlation with proteinuria. The proteinuria observed in BN and MAXX rats with autoantibodies to laminin 1 but no C3 in renal immune deposits likely is a direct consequence of autoantibody binding to the GBM. Antibodies alone, in the absence of complement, neutrophils, or other known secondary mediators, can cause glomerular injury and proteinuria (*29*). An alternative cause of proteinuria in DZB and PVG rats with renal immune deposits containing complement components is the activation of the classical complement pathway.

The histopathology of the renal damage caused by mercury-induced autoimmunity in BN, MAXX, and DZB rats is characterized by rather minor changes. An early publication reported various numbers of large mononuclear cells in glomeruli and focal detachment of glomerular endothelial cells as well as subendothelial and scattered subepithelial deposits (*207*). In our experiments with BN rats, the most prominent and frequent lesion was the detachment of endothelial cells from the GBM (*208*). Electron-opaque material, loose to compact floccular, was often present in the spaces created by the uplifting of the endothelial cells. These changes were observed in kidneys obtained on day 15 and day 30 of mercury treatment but were more pronounced in the latter. Occasionally, there was mesangial expansion of peripheral capillary loops with resulting splitting. Rare capillary loops showed small subepithelial electron-opaque deposits. To obtain more precise morphologic information, we examined kidneys

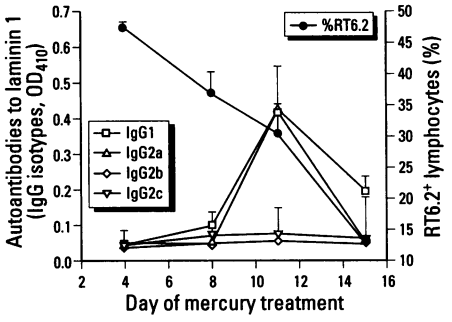

Figure 1. Mercury treatment induces the production of IgG1 and IgG2a autoantibodies to laminin 1, as detected by ELISA on day 11. The increase in serum autoantibody levels is negatively correlated with the decrease in the percent of RT6.2$^+$ T lymphocytes in peripheral lymph nodes.

from mercury-treated MAXX rats after *in vivo* perfusion with glutaraldehyde (*192*). Depending on the length of treatment, we observed two different histopathologic patterns. Kidneys obtained on the ninth day of mercury administration showed mild glomerular alterations, again with focal separation of endothelial cells from the GBM. No electron-opaque deposits were observed at that time. Kidneys obtained on day 32 showed increased separation of endothelial cells from the GBM with accumulation of flocculent electron-opaque material between the endothelial cells and the GBM. Some capillary loops showed thickening and splitting of the GBM with expansion of the mesangium. On both day 9 and day 32, visceral epithelial cells showed swelling of cell processes and focal foot process fusion. There were no subepithelial deposits or significant influx of inflammatory cells in the glomeruli. In conclusion, initial observations in mercury-injected BN rats may have led to the definition of the histopathology as a glomerulonephritis. However, as previously discussed for renal lesions induced in humans by mercury, the term may not be appropriate because of the lack of a strong inflammatory component. Better definitions may be membranous

glomerulonephropathy or membranous nephropathy.

Splenomegaly, lymph node hyperplasia, and thymic atrophy are detected in $HgCl_2$-treated BN rats. Extensive disorganization of the thymus, with loss of demarcation between cortex and medulla but without any detectable increase in apoptotic cells, occurs within 14 days of treatment (*209*). The numbers of thymus cells and the percentage of $CD8^+CD4^+$ double-positive thymocytes decreases, whereas the percentage of single-positive $CD8^+$ or $CD4^+$ and double-negative CD8-CD4- thymocytes increases (*209*). Total numbers of double-positive $CD8^+CD4^+$ thymocytes decrease, but total numbers of $CD4^+$ single-positive thymocytes increase. We have also observed that $HgCl_2$-treated BN rats have a decrease of $RT6^+$ T cells (*202,210*). Kinetic studies of this change have shown significant percentage decreases after 8, 11, and 15 days of $HgCl_2$ treatment and an inverse correlation with autoimmune responses to laminin 1 (Figure 1). Two-color flow cytometry has revealed that percentages of both $RT6.2^+CD4^+$ and $RT6.2^+CD8^+$ T lymphocytes decrease on day 15 of mercury treatment (*202*). Studies of diabetes-prone BB rats have suggested that $RT6^+$ T cells may have a still unexplained immunoregulatory role (*211–214*).

As previously mentioned, the histopathology observed by most investigators of this rat model is a membranous glomerulonephropathy without evident lesions in other tissues. More recently, inflammatory processes in various organs and tissues of mercury-treated BN rats have been reported. Inflammation and ulceration of the skin, hepatic periportal mononuclear cell infiltrates, and hemorrhagic lesions of the gut with intense submucosa inflammation and leucocytoclastic vasculitis have been observed (*215–219*). These rats produce antibodies to myeloperoxidase and develop a $CD8^+$ T-lymphocyte–mediated inflammatory polyarthritis. A focal inflammatory process of the parotid, submandibular, and lachrymal glands similar to the lesions of Sjögren's syndrome has also been detected in $HgCl_2$-treated BN rats (*220,221*). Because we had never observed any of these lesions, we recently re-examined a variety of tissues from various groups of BN rats injected with mercury. In spite of a very careful examination of plastic-embedded toluidine blue-stained sections as well as paraffin-embedded H&E-stained sections, we have not been able to detect inflammatory changes in thyroid, pancreas, intestine, skin, liver, parotid, and lung (*44*). At present, we cannot explain the difference in histopathology between our BN rats and those examined by other investigators. However, it has been reported that the inflammatory changes observed in various tissues disappear after antibiotic treatment, which suggests possible synergistic effects of mercury and microorganisms in rats that are not specific pathogen-free (*218*).

Cytokine profiles obtained using quantitative and semiquantitative PCR have suggested the hypothesis that an imbalance between T-helper (Th)1 and Th2 cells might be the basis of mercury-induced autoimmunity (*45,46*). Another approach to assess the *in vivo* functional effects of cytokines relies on the determination of immunoglobulin isotypes of autoantibodies. Autoantibodies to laminin 1 detected in $HgCl_2$-treated BN rats are of the IgG1 and IgG2a isotypes, confirming the suggestion of a polarized, type 2 cytokine profile in these animals (*193,201,202*). In contrast, after exposure to mercury, BB rats develop autoantibodies to laminin 1 of all IgG isotypes, including those likely dependent on Type 1 cytokines (*202*). These findings indicate that the type of cytokine production induced by mercury treatment may vary because of different immunogenetic and/or pharmacogenetic characteristics of each rat strain. Both MHC and non-MHC genes are important in autoimmune responses to mercury. BN and MAXX rats ($RT\text{-}1^n$ haplotype) have autoimmune responses to laminin 1 after mercury administration (*192,222*). Most other inbred rat strains, with the LEW ($RT\text{-}1^l$ haplotype) as the prototype, are resistant to these autoimmune effects (*222*). Particularly relevant in this regard are the findings in mercury-treated BN.1L and LEW.1N rats (i.e., animals that are congenic between the responder BN and the resistant LEW). None of these rats exhibit autoimmune responses to laminin, renal immune deposits, or proteinuria (*204,223*). On the other hand, circulating autoantibodies to laminin and IgG deposits in renal GBM can be induced by exposure to mercury in BN→LEW.1N chimeras (*223*). This demonstrates that both MHC and non-MHC background genes must be present for the induction of autoimmunity by mercury.

Finally, an interesting aspect of mercury immunotoxicity are the suppressive effects of this metal on autoimmune disease experimentally induced in LEW rats. Mercury inhibits experimental Heymann's nephritis, autoimmune encephalomyelitis, and autoimmune uveitis in LEW rats. This suppression may occur through the stimulation of non-antigen-specific $CD8^+$ "suppressor/cytotoxic cells" T lymphocytes (*199*), a lack of balance between Th1 and Th2 cytokines (*47*), or the secretion of transforming growth factor-β by autoreactive anti-class II $CD4^+$ T cells (*224*). We have recently demonstrated that mercury had no inhibitory effects on the spontaneous development and progression of insulin-dependent diabetes mellitus and thyroiditis in diabetes-prone BB rats (*197*), which suggests that the immunosuppressive effects of $HgCl_2$ may be a characteristic unique to the LEW strain.

Conclusions

The clinical observations and animal experiments summarized in this review allow some considerations about renal autoimmunity associated with metals. There is no doubt that exposure to gold and mercury can cause autoimmune responses in humans. A clear-cut correlation between administration of these metals and development of autoimmune responses has also been established by studies of experimental animals. In general, metal-induced autoimmune responses can either be harmless or result in autoimmune disease, depending on variables that are still unclear. The role of genetic factors is obviously very important in mouse and rat models of metal-induced autoimmunity. However, we still lack a precise definition of the immunogenetic, pharmacogenetic (ecogenetic), or other genetically determined conditions involved in the development of human autoimmunity caused by metals. Even the animal models have unexplained aspects. The administration of silver compounds to inbred mice induces the production of autoantibodies to fibrillarin that for unknown reasons do not cause the deposition of immune complexes in the kidney or result in other tissue damage. In contrast, autoantibodies induced by gold and mercury can form immune complexes in the kidney and cause renal pathology. The role of inflammatory cytokines and/or cytotoxic T cells in animals and humans exposed to metals is also unclear (*225,226*).

Xenobiotic-induced autoimmunity often differs from idiopathic or spontaneously occurring autoimmunity, as demonstrated by the toxic oil syndrome and the eosinophilia-myalgia syndrome. These disorders were characterized by a variety of autoimmune responses, but their clinical manifestations differed from idiopathic autoimmune disease (*227*). There are also notable clinical and laboratory discrepancies between drug-related lupus and SLE (*227,228*). On the contrary, autoimmune diseases induced by penicillamine (SLE, pemphigus, myasthenia gravis) are identical or quite similar to the corresponding idiopathic disorders (*42*). Gold- and mercury-induced renal disease has a pathology comparable to membranous glomerulonephropathy due to other causes or of idiopathic nature. We still do not know the autoantigens involved in autoimmune responses induced in humans by these metals, but mouse and rat models suggest that they may be laminin 1, fibrillarin, and nuclear histones.

It should also be stressed that animal models of metal-induced autoimmunity are not exactly comparable to human disease. The

systemic autoimmune responses induced by gold and mercury in rabbits, rats, and mice are different from those of human SLE. As mentioned above, BN rats treated with mercury produce autoantibodies to laminin 1. There is a good correlation between levels of these autoantibodies and proteinuria. Other autoantibodies (including anti-DNA antibodies) that have been detected in these rats are not associated with functional or morphologic kidney damage. In addition, the specificity of anti-DNA antibodies present in mercury-injected BN rats may be questionable, as polyreactive antibodies have been identified in some animals (*229*). Mercury-treated SJL mice produce autoantibodies to a nucleolar antigen, fibrillarin, similarly to some patients with scleroderma. SLE patients make autoantibodies to a variety of autoantigens but do not usually develop clinically relevant levels of antifibrillarin or antilaminin antibodies. The most likely pathogenic autoantibodies in SLE patients are directed against epitopes of double-stranded DNA and various ribosomal antigens (*186,230–232*). Thus, mercury does not seem to induce an SLE-like syndrome in rats or mice. The xenobiotic-induced animal model that most resembles SLE may very well be the autoimmune disease caused by pristane in some inbred strains of mice. SJL/J mice treated with this xenobiotic develop autoantibodies to ribosomal P antigens (a lupus-related specificity) and immune complex glomerulonephritis (*233*). Pristane-treated BALB/c mice develop rheumatoid factor-positive erosive arthritis and a lupuslike syndrome characterized by immune complex-mediated glomerulonephritis and circulating autoantibodies to nRNP/Sm, Su, and single-stranded DNA (*233*).

As mentioned at the beginning of this review, SLE is characterized by a wide spectrum of renal pathologic changes, from mesangial and membranous nephropathy to severe glomerulonephritis, often leading to sclerosing nephropathy (*23,234,235*). Renal manifestations in patients with systemic sclerosis are caused by arterial and glomerular lesions, with fibrinoid necrosis and fibrotic changes (*236*). In contrast, the renal histopathology observed in rat models of mercury autoimmunity shows scarce alterations of kidney structures, lacks major inflammatory reactions, and is usually defined as a membranous nephropathy, not a glomerulonephritis (*201*). Similarly, both immunohistopathology and histopathology of mercury-induced autoimmunity in SJL mice reveal immune deposits at the mesangial level, expanded glomerular mesangial zones with electron-opaque deposits, and a moderate increase of endocapillary cells (*178,188*). The absence of inflammatory or other major structural changes suggests that this pathology is best described by the term mesangial glomerulonephropathy.

In both rats and mice, mercury treatment causes a nephrotic syndrome, i.e., abundant proteinuria. BN, MAXX, and DZB rats produce autoantibodies against laminin 1, a component of the renal GBM. These autoantibodies likely have a pathogenetic role and may cause proteinuria through direct autoantibody effects or activation of the complement cascade. PVG rats and SJL mice treated with mercury may develop proteinuria because of renal immune deposits containing autoantibodies to nuclear and nucleolar antigens plus complement components. As previously mentioned, both cytotoxic T lymphocytes and cytokine-producing T lymphocytes and macrophages may cause additional damage, but to date there is no solid evidence in favor of such effects.

Autoimmune responses and renal disease caused in humans by gold and mercury usually end after withdrawal of the metal. Animal models differ depending on the species. Mercury-induced autoimmunity in BN and MAXX rats develops rapidly and spontaneously terminates within a month even if the administration of the metal is continued. Instead, mice need a much longer time of exposure to mercury for the development of autoimmune responses but continue producing autoantibodies to fibrillarin for up to 12 months after mercury treatment is interrupted.

The issue of facilitation versus *de novo* induction of autoimmunity often arises and has no easy answer. A relatively short period of exposure to a metal may suggest facilitation of an underlying disease. *De novo* induction of autoimmunity may be implied by a longer period. Lithium seems to facilitate autoimmunity in individuals that have either low-grade or initial thyroid disease. Mercury may both facilitate and induce autoimmunity *de novo*. The administration of $HgCl_2$ to $(NZB \times NZW)F_1$ mice, susceptible to murine lupus, stimulates a polyclonal B-cell activation, with high levels of IgG1, IgG3, and IgE immunoglobulins, and intense autoantibody production against double-stranded DNA, IgG, and collagen (*153*). Similarly, mercury treatment facilitates autoimmune responses to thyroglobulin and laminin 1 in BB rats, susceptible to develop insulin-dependent diabetes mellitus and thyroiditis (*197*). In addition, gold and mercury can induce autoimmunity *de novo* in outbred rabbits and guinea pigs as well as inbred rat and mouse strains that do not spontaneously develop autoimmune responses and disease.

Another issue of particular interest and difficult solution is the role of certain structure–activity relationships in gold- and mercury-induced autoimmunity. A possible role of the interaction with thiols was initially suggested by studies with penicillamine and gold compounds. Gold, mercury, and silver have high affinities for thiol groups and the formation of disulfide bonds between -SH groups and thiols of self-proteins might alter the structure of autoantigens or reveal hidden epitopes. Changes in fibrillarin epitopes caused by mercury treatment have been recently demonstrated (*237*). In addition, metals might form disulfide bonds with cell surface structures and activate immune cells. Unfortunately, this issue is complicated by other metals such as lead, copper, and cadmium that have affinity for thiol groups but do not usually induce autoimmune responses.

The limited percentage of human subjects developing autoimmunity after exposure to gold or mercury has a parallel in early experimental studies showing that relatively small percentages of outbred animals exhibited autoimmunity after treatment with these metals. The genetic makeup of human populations is usually quite diverse; therefore, it is not surprising that renal autoimmunity induced by metals is not a common occurrence (*173*). More recent laboratory investigations have discovered that gold and mercury cause autoimmunity only in a few strains of inbred mice and rats. The penetrance of mercury- and gold-induced autoimmune disease in these susceptible inbred strains reaches 100%. Most other inbred strains are completely resistant to the autoimmune effects of mercury and gold. These observations have suggested that immunogenetic and pharmacogenetic (ecogenetic) factors are necessary for the expression of autoimmune disease induced by mercury and other metals (*39,43,44*). If such susceptible genotypes exist in humans, only a small percentage of metal-exposed individuals is likely to develop autoimmune disease.

As previously mentioned, it is difficult to evaluate whether human autoimmunity is caused by an environmental metal, especially when multiple xenobiotics are involved, the initial exposure did not occur in the workplace, or the exposure happened in the distant past. In this respect great help is provided by the various animal models, as researchers know the metal involved as well as the initial time and dose of exposure. However, the molecular, biochemical, and cellular events involved in the induction of metal-induced autoimmunity are still unclear. Gold and mercury may cause autoimmune responses by their effects that can stimulate the immune system following indirect or direct pathways (Table 8) (*39,44,48,110*). We have previously mentioned that these metals, acting on tissues and organs of the body, may modify autoantigen structure and expose new or cryptic epitopes. A good example is provided by the interaction of mercury with the autoantigen fibrillarin, changing its molecular

Table 8. Summary of gold and mercury effects that may lead to autoimmunity.

Indirect pathway	Direct pathway
Modification of autoantigen structure (exposing new or cryptic epitopes)	Activity as immunogen
Release of nuclear autoantigens	Mitogenic effects on T cells
Release of nucleolar autoantigens	Sequential activation of T-helper lymphocytes (Th2 > Th1 ? ; other ?)
Release of cytoplasmic autoantigens	Stimulation of B lymphocytes
Release of extracellular matrix components	Activation of macrophages and other antigen-presenting cells
Upregulation of stress proteins (?)	Upregulation of costimulatory pathways and adhesion molecules
Molecular mimicry between epitopes of metal and host autoantigens (?)	Inhibition of immunoregulatory cells (?)

Abbreviations: ?, needs additional evidence; Th, T helper.

and antigenic properties. Mercury can also induce the expression of heat shock proteins (stress proteins) and/or release cellular or extracellular matrix components. Gold and mercury can directly activate the immune system by stimulating immune cells or acting as immunogens or haptens. They may affect Th cells, regulatory T lymphocytes, and B lymphocytes, and upregulate costimulatory pathways and adhesion molecules. Finally, metals may favor epitope presentation by macrophages and other antigen-presenting cells and stimulate their cytokine production. Changes in the cytokine network and loss of immune tolerance to autoantigens are likely consequences of these interactions between heavy metals and cells of the immune system. Increased levels of IgE and IgG1 in mercury-treated rats and mice as well as initial results using antibodies to IL-4 suggested that this cytokine might be an important mediator of T-cell-dependent B-cell activation (*148*). In this view, mercury would cause a lack of balance between Th1 and Th2 cells (*45,46, 93,238*). However, recent experiments in cytokine-knockout mice treated with mercury have not confirmed this hypothesis and have shown that IL-4 is not required, whereas IFN-γ is essential for the production of autoantibodies to fibrillarin (*239*). IFN-γ may be necessary to stimulate immune responses to self-antigens, possibly through the increase in MHC class II and class I expression (facilitating epitope presentation) and/or the induction of costimulatory factors. Once autoimmunity is initiated, it may eventually develop in type 2 and/or type 1 cytokine-regulated responses, depending on cytokine level and balance, costimulatory molecules, autoantigen structure, and concentration and other environmental factors.

In conclusion, a single mechanism is unlikely to be responsible for the induction of autoimmune responses and disease by metals. Studies of these complex events are obviously difficult and may only be helped by in-depth investigations of animal models, that allow better control of some variables involved in the autoimmune process. Because of its diverse immunotoxic properties, mercury should be considered a paradigm of metal-induced autoimmunity (*44*). *In vitro* and *in vivo* research of autoimmune disease caused by mercury, gold, and other metals has already yielded extremely valuable information and answered a number of important questions. At the same time it has raised various issues about possible immunostimulatory or immunosuppressive mechanisms of xenobiotic activity. Thus it is evident that investigations of metal-induced autoimmunity have the potential to produce new knowledge with relevance both to autoimmune disease caused by xenobiotics in general and to idiopathic autoimmunity.

References and Notes

1. Schwartz MM. The pathologic diagnosis of renal disease. In: Heptinstall's Pathology of the Kidney (Jennette JC, Olson JL, Schwartz MM, Silva FG, eds). Philadelphia:Lippincott-Raven Publishers, 1998;169–180.
2. Silva FG. Acute postinfectious glomerulonephritis and glomerulonephritis complicating persistent bacterial infection. In: Heptinstall's Pathology of the Kidney (Jennette JC, Olson JL, Schwartz MM, Silva FG, eds). Philadelphia:Lippincott-Raven Publishers, 1998;389–453.
3. Rodríguez-Iturbe B. Acute endocapillary glomerulonephritis. In: Oxford Textbook of Clinical Nephrology (Davison AM, Cameron JS, Grünfeld J-P, Kerr DNS, Ritz E, Winearls CG, eds). Oxford, UK:Oxford University Press, 1998;613–624.
4. Rees AJ, Cameron JS. Crescentic glomerulonephritis. In: Oxford Textbook of Clinical Nephrology (Davison AM, Cameron JS, Grünfeld J-P, Kerr DNS, Ritz E, Winearls CG, eds). Oxford, UK:Oxford University Press, 1998;625–646.
5. Turner AN, Rees AJ. Antiglomerular basement membrane disease. In: Oxford Textbook of Clinical Nephrology (Davison AM, Cameron JS, Grünfeld J-P, Kerr DNS, Ritz E, Winearls CG, eds). Oxford, UK:Oxford University Press, 1998;646–666.
6. Meyers CM, Kalluri R, Neilson EG. Anti-glomerular basement membrane disease. In: Immunologic Renal Disease (Neilson EG, Couser WG, eds). Philadelphia:Lippincott-Raven Publishers, 1997;959–973.
7. Jennette JC. Crescentic glomerulonephritis. In: Heptinstall's Pathology of the Kidney (Jennette JC, Olson JL, Schwartz MM, Silva FG, eds). Philadelphia:Lippincott-Raven Publishers, 1998;625–656.
8. Falk RJ, Jennette JC. Renal vasculitis. In: Immunologic Renal Disease (Neilson EG, Couser WG, eds). Philadelphia:Lippincott-Raven Publishers, 1997;1099–1118.
9. Cameron JS. The patient with proteinuria and/or haematuria. In: Oxford Textbook of Clinical Nephrology (Davison AM, Cameron JS, Grünfeld J-P, Kerr DNS, Ritz E, Winearls CG, eds). Oxford, UK:Oxford University Press, 1998;441–459.
10. Cameron JS. The nephrotic syndrome: management, complications, and pathophysiology. In: Oxford Textbook of Clinical Nephrology (Davison AM, Cameron JS, Grünfeld J-P, Kerr DNS, Ritz E, Winearls CG, eds). Oxford, UK:Oxford University Press, 1998;461–492.
11. Meyers KEC, Kujubu DA, Kaplan BS. Minimal-change nephrotic syndrome. In: Immunologic Renal Disease (Neilson EG, Couser WG, eds). Philadelphia:Lippincott-Raven Publishers, 1997;975–992.
12. Broyer M, Meyrier A, Niaudet P, Habib R. Minimal changes and focal segmental glomerular sclerosis. In: Oxford Textbook of Clinical Nephrology (Davison AM, Cameron JS, Grünfeld J-P, Kerr DNS, Ritz E, Winearls CG, eds). Oxford, UK:Oxford University Press, 1998;493–535.
13. Olson JL, Schwartz MM. The nephrotic syndrome: minimal change disease, focal segmental glomerulosclerosis, and miscellaneous causes. In: Heptinstall's Pathology of the Kidney (Jennette JC, Olson JL, Schwartz MM, Silva FG, eds). Philadelphia:Lippincott-Raven Publishers, 1998;187–257.
14. Cattell V, Jennette JC. Mechanisms of acute inflammatory and immunologic renal injury. In: Heptinstall's Pathology of the Kidney (Jennette JC, Olson JL, Schwartz MM, Silva FG, eds). Philadelphia:Lippincott-Raven Publishers, 1998;85–136.
15. Couser WG, Alpers CE. Membranous nephropathy. In: Immunologic Renal Disease (Neilson EG, Couser WG, eds). Philadelphia:Lippincott-Raven Publishers, 1997;1027–1052.
16. Zucchelli P, Pasquali S. Membranous nephropathy. In: Oxford Textbook of Clinical Nephrology (Davison AM, Cameron JS, Grünfeld J-P, Kerr DNS, Ritz E, Winearls CG, eds). Oxford, UK:Oxford University Press, 1998;571–590.
17. Schwartz MM. Membranous glomerulonephritis. In: Heptinstall's Pathology of the Kidney (Jennette JC, Olson JL, Schwartz MM, Silva FG, eds). Philadelphia:Lippincott-Raven Publishers, 1998;259–307.
18. Miller RB, Kashtan CE, Burke BA, Kim Y. Idiopathic membranoproliferative glomerulonephritis. In: Immunologic Renal Disease (Neilson EG, Couser WG, eds). Philadelphia:Lippincott-Raven Publishers, 1997;1133–1145.
19. Williams DG. Mesangiocapillary glomerulonephritis. In: Oxford Textbook of Clinical Nephrology (Davison AM, Cameron JS, Grünfeld J-P, Kerr DNS, Ritz E, Winearls CG, eds). Oxford, UK:Oxford University Press, 1998;591–612.
20. Silva FG. Membranoproliferative glomerulonephritis. In: Heptinstall's Pathology of the Kidney (Jennette JC, Olson JL, Schwartz MM, Silva FG, eds). Philadelphia:Lippincott-Raven Publishers, 1998;309–368.
21. Silva FG. Mesangial proliferative glomerulonephritis. In: Heptinstall's Pathology of the Kidney (Jennette JC, Olson JL, Schwartz MM, Silva FG, eds). Philadelphia:Lippincott-Raven Publishers, 1998;455–478.
22. Cameron JS. Systemic lupus erythematosus. In: Immunologic Renal Disease (Neilson EG, Couser WG, eds). Philadelphia: Lippincott-Raven Publishers, 1997;1055–1098.
23. Ponticelli C, Banfi G, Moroni G. Systemic lupus erythematosus (clinical). In: Oxford Textbook of Clinical Nephrology (Davison AM, Cameron JS, Grünfeld J-P, Kerr DNS, Ritz E, Winearls CG, eds). Oxford, UK:Oxford University Press, 1998; 935–959.
24. D'Agati VD. Renal disease in systemic lupus erythematosus, mixed connnective tissue disease, Sjögren's syndrome, and rheumatoid arthritis. In: Heptinstall's Pathology of the Kidney (Jennette JC, Olson JL, Schwartz MM, Silva FG, eds). Philadelphia:Lippincott-Raven Publishers, 1998;541–624.
25. Cavallo T. Tubulointerstitial nephritis. In: Heptinstall's Pathology of the Kidney (Jennette JC, Olson JL, Schwartz MM, Silva FG, eds). Philadelphia:Lippincott-Raven Publishers, 1998;667–723.
26. Strutz F, Müller CA, Müller GA. Mechanisms of interstitial inflammation. In: Oxford Textbook of Clinical Nephrology (Davison AM, Cameron JS, Grünfeld J-P, Kerr DNS, Ritz E, Winearls CG, eds). Oxford, UK:Oxford University Press, 1998;1113–1127.
27. Appel GB. Acute interstitial nephritis. In: Immunologic Renal Disease (Neilson EG, Couser WG, eds). Philadelphia:Lippincott-Raven Publishers, 1997;1221–1234.
28. Abrass CK. Mechanisms of immune complex formation and deposition in renal structures. In: Immunologic Renal Disease (Neilson EG, Couser WG, eds). Philadelphia:Lippincott-Raven Publishers, 1997;291–307.
29. Salant DJ, Natori Y, Shimizu F. Glomerular injury due to antibody alone. In: Immunologic Renal Disease (Neilson EG, Couser WG, eds). Philadelphia:Lippincott-Raven Publishers, 1997;359–375.
30. Johnson RJ, Klebanoff SJ, Couser WG. Neutrophils. In: Immunologic Renal Disease (Neilson EG, Couser WG, eds). Philadelphia:Lippincott-Raven Publishers, 1997;547–559.
31. Nikolic-Paterson DJ, Lan HY, Atkins RC. Macrophages in immune renal injury. In: Immunologic Renal Disease (Neilson EG, Couser WG, eds). Philadelphia:Lippincott-Raven Publishers, 1997;575–592.

32. Floege J, Rees AJ. Growth factors and cytokines. In: Immunologic Renal Disease (Neilson EG, Couser WG, eds). Philadelphia:Lippincott-Raven Publishers, 1997;417–454.
33. Wilson CB. Autoimmune renal disease. In: The Molecular Pathology of Autoimmune Disease (Bona CA, Siminovitch K, Theofilopoulos AN, Zanetti M, eds). Chur, Switzerland:Harwood Academic Publishers, 1993;673–704.
34. Wilson CB. Immune models of glomerular injury. In: Immunologic Renal Disease (Neilson EG, Couser WG, eds). Philadelphia:Lippincott-Raven Publishers, 1997;729–773.
35. Wilson CB. Immune models of tubulointerstitial injury. In: Immunologic Renal Disease (Neilson EG, Couser WG, eds). Philadelphia:Lippincott-Raven Publishers, 1997;775–799.
36. Racusen LC. Autoimmune diseases in the kidney. In: The Autoimmune Diseases (Rose NR, Mackay I, eds). San Diego:Academic Press, 1998;603–621.
37. Friedman H, Rose NR, Bendinelli M, eds. Microorganisms and Autoimmune Diseases. New York:Plenum Press, 1996.
38. Harrison LC, McColl GJ. Infection and autoimmune disease. In: The Autoimmune Diseases (Rose NR, Mackay I, eds). San Diego:Academic Press, 1998;127–140.
39. Bigazzi PE. Autoimmunity caused by xenobiotics. Toxicology 119:1–21 (1997).
40. Bigazzi PE. Autoimmunity induced by chemicals. J Toxicol Clin Toxicol 26:125–156 (1988).
41. Bigazzi PE. Autoimmunity and heavy metals. Lupus 3:449–453 (1994).
42. Kosuda LL, Bigazzi PE. Chemical-induced autoimmunity. In: Experimental Immunotoxicology (Smialowicz RJ, Holsapple MP, eds). Boca Raton, FL:CRC Press, 1996;419–465.
43. Bigazzi PE. Autoimmunity induced by metals. In: Toxicology of Metals (Chang LW, ed). Boca Raton, FL:CRC Lewis Publishers, 1996;835–852.
44. Bigazzi PE. Mercury. In: Immunotoxicology of Environmental and Occupational Metals (Zelikoff J, Thomas P, eds). London:Taylor & Francis, 1998;131–161.
45. Druet P, Sheela R, Pelletier L. TH1 and TH2 lymphocytes in autoimmunity. Adv Nephrol 25:217–241 (1996).
46. Druet P, Sheela R, Pelletier L. Th1 and Th2 cells in autoimmunity. Chem Immunol 63:158–170 (1996).
47. Druet P, Pelletier L. Th2 and Th1 autoreactive anti-class II cell lines in the rat suppress or induce autoimmunity. J Autoimmun 9:221–226 (1996).
48. Griem P, Gleichmann E. Metal ion induced autoimmunity. Curr Opinion Immunol 7:831–838 (1995).
49. Pollard KM, Hultman P. Effects of mercury on the immune system. In: Metal Ions in Biological Systems (Sigel A, Sigel H, eds). New York:Marcel Dekker, 1997;421–440.
50. Yoshida S, Gershwin ME. Autoimmunity and selected environmental factors of disease induction. Semin Arthritis Rheum 22:399–419 (1993).
51. Kreiss K, Miller F, Newman LS, Ojo-Amaize EA, Rossman MD, Saltini C. Chronic beryllium disease—from the workplace to cellular immunology, molecular immunogenetics, and back. Clin Immunol Immunopathol 71:123–129 (1994).
52. Smialowicz RJ. Nickel. In: Immunotoxicology of Environmental and Occupational Metals (Zelikoff J, Thomas P, eds). London:Taylor & Francis, 1998;163–194.
53. Cohen MD. Vanadium. In: Immunotoxicology of Environmental and Occupational Metals (Zelikoff J, Thomas P, eds). London:Taylor & Francis, 1998;207–229.
54. Cohen MD. Immunotoxicology summary tables. In: Immunotoxicology of Environmental and Occupational Metals (Zelikoff J, Thomas P, eds). London:Taylor & Francis, 1998;263–359.
55. Omara FO, Brousseau P, Blakley BR, Fournier M. Iron, zinc, and copper. In: Immunotoxicology of Environmental and Occupational Metals (Zelikoff J, Thomas P, eds). London:Taylor & Francis, 1998;231–262.
56. Koller LD. Cadmium. In: Immunotoxicology of Environmental and Occupational Metals (Zelikoff J, Thomas P, eds). London:Taylor & Francis, 1998;41–61.
57. Bernard AM, Roels HR, Foidart JM, Lauwerys RL. Search for anti-laminin antibodies in the serum of workers exposed to cadmium, mercury vapour or lead. Int Arch Occup Environ Health 59:303–309 (1987).
58. Cardenas A, Roels HR, Bernard AM, Foidart JM, Lauwerys RL. Markers of early renal changes induced by industrial pollutants. I: Application to workers exposed to mercury vapour. Br J Ind Med 50:17–27 (1993).
59. Ellingsen DG, Gaarder PI, Kjuus H. An immunological study of chloralkali workers previously exposed to mercury vapour. Acta Pathol Microbiol Immunol Scand 102:170–176 (1994).
60. Zelikoff JT, Cohen MD. Immunotoxicology of inorganic metal compounds. In: Experimental Immunotoxicology (Smialowicz RJ, Holsapple MP, eds). Boca Raton, FL:CRC Press, 1996;89–228.
61. Kilburn KH, Warshaw RH. Prevalence of symptoms of systemic Llupus erythematosus (SLE) and of fluorescent antinuclear antibodies associated with chronic exposure to trichloroethylene and other chemicals in well water. Environ Res 57:1–9 (1992).
62. Tsankov N, Stransky L, Kostowa M, Mitrowa T, Obreschkowa E. Induced pemphigus caused by occupational contact with Basochrom. Dermatosen Beruf Umwelt - Occup Environ Dermat 38:91–93 (1990).
63. Pocino M, Malavé I, Baute L. Zinc administration restores the impaired immune response observed in mice receiving excess copper by oral route. Immunopharmacol Immunotoxicol 12:697–713 (1990).
64. McCabe MJJ. Lead. In: Immunotoxicology of Environmental and Occupational Metals (Zelikoff J, Thomas P, eds). London:Taylor & Francis, 1998;111–130.
65. El-Fawal HAN. Concepts of immunological biomarkers of metal toxicity. In: Toxicology of Metals (Chang LW, ed). Boca Raton, FL:CRC Lewis Publishers, 1996;861–869.
66. Rodgers K. Platinum. In: Immunotoxicology of Environmental and Occupational Metals (Zelikoff J, Thomas P, eds). London:Taylor & Francis, 1998;195–206.
67. Schuppe H-C, Ronnau AC, von Schmiederberg S, Ruzicka T, Gleichmann E, Griem P. Immunomodulation by heavy metal compounds. Clin Dermatol 16:149–157 (1998).
68. Stein EC, Schiffer RB, Hall WJ, Young N. Multiple sclerosis and the workplace: report of an industry-based cluster. Neurology 37:1672–1677 (1987).
69. Schiffer RB, Herndon RM, Stabrowski A. Effects of dietary trace metals on experimental allergic encephalomyelitis in SJL mice. Ann Neurol 24:141 (1988).
70. Schiffer RB, Herndon RM, Eskin T. Effects of altered dietary trace metals upon experimental allergic encephalomyelitis. Neurotoxicology 11:443–450 (1990).
71. Schiffer RB, Sunderman FWJ, Baggs RB, Moynihan JA. The effects of exposure to dietary nickel and zinc upon humoral and cellular immunity in SJL mice. J Neuroimmunol 34:229–239 (1991).
72. Hollinger MA. Toxicological aspects of topical silver pharmaceuticals. Crit Rev Toxicol 26:255–260 (1996).
73. Hultman P, Enestrom S, Turley SJ, Pollard KM. Selective induction of anti-fibrillarin autoantibodies by silver nitrate in mice. Clin Exp Immunol 96:285–291 (1994).
74. Hultman P, Johansson U, Turley SJ, Lindh U, Enestrom S, Pollard KM. Adverse immunological effects and autoimmunity induced by dental amalgam and alloy in mice. FASEB J 8:1183–1190 (1994).
75. Hultman P, Ganowiak K, Turley SJ, Pollard KM. Genetic susceptibility to silver-induced anti-fibrillarin autoantibodies in mice. Clin Immunol Immunopathol 77:291–297 (1995).
76. Hart DA. Modulation of the immune system elements by lithium. In: Lithium and Cell Physiology (Bach RO, Gallicchio VS, eds). New York:Springer-Verlag, 1990;58–81.
77. Hart DA. Lithium, lymphocyte stimulation and the neuroimmune interface. Lithium Ther Monogr 4:46–67 (1991).
78. Hassman RA, McGregor AM. Lithium and autoimmune thyroid disease. Lithium Ther Monogr 2:134–146 (1988).
79. Hassman R, Solic N, Jasani B, Hall R, McGregor AM. Immunological events leading to destructive thyroiditis in the AUG rat. Clin Exper Immunol 73:410–416 (1988).
80. Tishler M, Nyman J, Wahren M, Yaron M. Anti-Ro (SSA) antibodies in rheumatoid arthritis patients with gold-induced side effects. Rheumatol Int 17:133–135 (1997).
81. Kosty MP, Hench PK, Tani P, McMillan R. Thrombocytopenia associated with auronofin therapy: evidence for a gold-dependent immunologic mechanism. Am J Hematol 30:236–239 (1989).
82. Pedersen-Bjergaard U, Andersen M, Hansen PB. Thrombocytopenia induced by noncytotoxic drugs in Denmark 1968–91. J Intern Med 239:509–515 (1996).
83. Tournade H, Guery JC, Pasquier R, Vial MC, Mandet C, Druet E, Dansette PM, Druet P, Pelletier L. Effect of the thiol group on experimental gold-induced autoimmunity. Arthritis Rheum 34:1594–1599 (1991).
84. Tournade H, Guery J-C, Pasquier R, Nochy D, Hinglais N, Guilbert B, Druet P, Pelletier L. Experimental gold-induced autoimmunity. Nephrol Dial Transplant 6:621–630 (1991).
85. Törnroth T, Skrifvars B. Gold nephropathy prototype of membranous glomerulonephritis. Am J Pathol 75:573–586 (1974).
86. Fillastre J-P, Godin M. Drug-induced nephropathies. In: Oxford Textbook of Clinical Nephrology (Davison AM, Cameron S, Grünfeld J-P, Kerr D, Ritz E, Wonearls CG, eds). Oxford, UK:Oxford University Press, 1998;2645–2657.
87. Barr RD, Rees PH, Cordy PE, Kungu A, Woodger BA. Nephrotic syndrome in adult Africans in Nairobi. Br Med J 2:131–134 (1972).
88. Barr RD, Woodger BA, Rees PH. Levels of mercury in urine correlated with the use of skin lightening creams. Am J Clin Pathol 59:36–40 (1973).
89. Lindqvist KJ, Makene WJ, Shaba JK, Nantulya V. Immunofluorescence and electron microscopic studies of kidney biopsies from patients with nephrotic syndrome, possibly induced by skin lightening creams containing mercury. E Afr Med J 51:168–169 (1974).
90. Charpentier B, Moullot P, Faux N, Manigand G, Fries D. Fonctions lymphocytaires T au cours d'une glomérulonéphrite extramembraneuse induite par une intoxication chronique au mercure. Néphrologie 2:153–157 (1981).
91. Schrallhammer-Benkler K, Ring J, Przybilla B, Landthaler M. Acute mercury intoxication with lichenoid drug eruption followed by mercury contact allergy and development of antinuclear antibodies. Acta Derm Venereol (Stockholm) 72:294–296 (1992).
92. Röger J, Zillikens D, Burg G, Gleichmann E. Systemic autoimmune disease in a patient with long-standing exposure to mercury. Eur J Dermat 2:168–170 (1992).
93. Mathieson PW. Mercury: god of Th2 cells? Clin Exp Immunol 102:229–230 (1995).
94. Hart DA. Immunoregulation in patients treated with lithium for affective disorders. Lithium Ther Monogr 4:68–78 (1991).
95. Tam VK, Green J, Schwieger J, Cohen AH. Nephrotic syndrome and renal insufficiency associated with lithium therapy. Am J Kidney Dis 27:715–720 (1996).
96. Merchant B. Gold, the noble metal and the paradoxes of its toxicology. Biologicals 26:49–59 (1998).
97. Hostynek JJ. Gold: an allergen of growing significance. Food Chem Toxicol 35:839–844 (1997).
98. Hamada R, Osame M. Minamata disease and other mercury syndromes. In: Toxicology of Metals (Chang LW, ed). Boca Raton, FL:CRC Lewis Publishers, 1996;337–351.
99. Kirchner J, Stein A, Viel K, Jacobi V. Hamman-Rich-Syndrom bei einem Goldschmied. Aktuelle Radiol 7:321–323 (1997).
100. Smith W, Ball GV. Lung injury due to gold treatment. Arthritis Rheum 23:351–354 (1980).
101. Nagi AH, Khan AH. Gold nephropathy in rabbits using an indigenous preparation. A morphological study. Intern Urol Nephrol 16:49–59 (1984).
102. Descotes J. Immunotoxicology of drugs and chemicals. New York:Elsevier, 1986.
103. Zürcher K, Krebs A. Cutaneous Drug Reactions. Basel:Karger, 1992.
104. van der Voet GB, de Wolff FA. Human exposure to lithium, thallium, antimony, gold, and platinum. In: Toxicology of Metals (Chang LW, ed). Boca Raton, FL:CRC Lewis Publishers, 1996;455–460.
105. Russell MA, Langley M, Truett AP, King LEJ, Boyd AS. Lichenoid dermatitis after consumption of gold-containing liquor. J Am Acad Dermatol 36:841–844 (1997).
106. Gordon DA. Gold compounds and penicillamine in the rheumatic diseases. In: Textbook of Rheumatology (Kelley WN, Harris EDJ, Ruddy S, Sledge CB, eds). Philadelphia:W.B. Saunders, 1997;759–769.
107. Jones G, Brooks PM. Injectable gold compounds: an overview. Br J Rheumatol 35:1154–1158 (1996).
108. Kean WF, Hart L, Buchanan WW. Auranofin. Br J Rheumatol 36:560–572 (1997).
109. Handel ML. Transcription factors AP-1 and NFkB: where steroids meet the gold standard of anti-rheumatic drugs. Inflamm Res 46:282–286 (1997).
110. Griem P, Wulferink M, Sachs B, González JB, Gleichmann E. Allergic and autoimmune reactions to xenobiotics: how do they arise? Immunol Today 19:133–141 (1998).
111. Ward PA, Goldschmidt P, Greene ND. Suppressive effects of metal salts on leukocyte and fibroblastic functions. J Reticuloendoth Soc 18:313–321 (1975).
112. Zalewski PD, Forbes IJ, Valente L, Hurst NP. Auranofin increases the affinity of phorbol dibutyrate receptors in chronic lymphocytic leukemia cells (B cells). J Immunol 138:3005–3009 (1987).
113. Griem P, Takahashi K, Kalbacher H, Gleichmann E. The antirheumatic drug disodium aurothiomalate inhibits CD4+ T cell recognition of peptides containing two or more cysteine residues. J Immunol 155:1575–1587 (1995).
114. Goebel C, Kubicka-Muranyi M, Tonn T, Gonzalez J, Gleichmann E. Phagocytes render chemicals immunogenic: oxidation of gold(I) to the T cell-sensitizing gold(III) metabolite generated by mononuclear phagocytes. Arch Toxicol 69:450–459 (1995).

115. Griem P, Gleichmann E. Das Antirheumatikum Gold: Erwunschte und unerwunschte Wirkungen von Au(I) und Au(III) auf das Immunsystem. Z Rheumatol 55:348–358 (1996).
116. Chong BH. Drug-induced immune thrombocytopenia. Platelets 2:173–181 (1991).
117. Salama A, Mueller-Eckardt C. Immune-mediated blood cell dyscrasia related to drugs. Semin Hematol 29:54–63 (1992).
118. von dem Borne AEGK, Pegels JG, van der Stadt RJ, van der Plasvan Dalen CM, Helmerhorst FM. Thrombocytopenia associated with gold therapy: a drug induced autoimmune disease? Br J Haematol 63:509–516 (1986).
119. Lee JC, Dushkin M, Eyring EJ, Engleman EP, Hopper JJ. Renal lesions associated with gold therapy. Light and electron microscopic studies. Arthr Rheum 8:1–13 (1965).
120. Katz A, Little AH. Gold nephropathy. Arch Pathol 96:133–136 (1973).
121. Watanabe I, Whittier FC, Moore J, Cuppage FE. Gold nephropathy. Arch Pathol Lab Med 100:632–635 (1976).
122. Wooley PH, Griffin J, Panayi GS, Batchelor JR, Welsch KI, Gibson TJ. HLA-DR antigens and toxic reaction to sodium aurothiomalate and D-penicillamine in patients with rheumatoid arthritis. New Engl J Med 303:300–302 (1980).
123. Bardin L, Dryll A, Debeyre N. HLA system and side effects of gold and D-penicillamine treatment of rheumatoid arthritis. Ann Rheum Dis 41:599–601 (1982).
124. Gran JT, Husby G, Thorsby E. HLA-DR antigens and gold toxicity. Ann Rheum Dis 42:63–71 (1983).
125. Barger BO, Acton RT, Koopman WJ, Alarcon GS. DR antigens and gold toxicity in white rheumatoid arthritis patients. Arthritis Rheum 27:601–607 (1984).
126. Hall CL. Gold nephropathy. Nephron 50:265–272 (1988).
127. Hall CL. The natural course of gold and penicillamine nephropathy: a longterm study of 54 patients. Adv Exper Med Biol 252:247–256 (1989).
128. Quarenghi MI, Del Vecchio L, Casartelli D, Manunta P, Rossi R. MPO antibody-positive vasculitis in a patient with psoriatic arthritis and gold-induced membranous glomerulonephritis. Nephrol Dial Transplant 13:2104–2106 (1998).
129. Nagi AH, Alexander F, Barabas AZ. Gold nephropathy in rats. Light and electron microscopic studies. Exp Mol Pathol 15:354–362 (1971).
130. Ueda S, Wakashin M, Wakashin Y, Yoshida H, Iesato K, Mori T, Mori Y, Akikusa B, Okuda K. Experimental gold nephropathy in guinea pigs: detection of autoantibodies to renal tubular antigens. Kidney Int 29:539–548 (1986).
131. Goter-Robinson CJ, Balasz T, Egorov IK. Mercuric chloride, gold sodium thiomalate, and D-penicillamine induced antinucleolar antibodies in mice. Toxicol Appl Pharmacol 86:159–169 (1986).
132. Schuhmann D, Kubicka-Muranyi M, Mirtschewa J, Günther J, Kind P, Gleichmann E. Adverse immune reactions to gold. I. Chronic treatment with an Au(I) drug sensitizes mouse T cells not to Au(I), but to Au(III) and induces autoantibody formation. J Immunol 145:2132–2139 (1990).
133. Pietsch P, Vohr H-W, Degitz K, Gleichmann E. Immunological alterations inducible by mercury compounds. II: $HgCl_2$ and gold sodium thiomalate enhance serum IgE and IgG concentrations in susceptible mouse strains. Int Arch Allergy Appl Immunol 90:47–53 (1989).
134. Qasim FJ, Thiru S, Gillespie K. Gold and D-penicillamine induce vasculitis and up-regulate mRNA for IL-4 in the Brown Norway rat: support for a role for Th2 cell activity. Clin Exp Immunol 108:438–445 (1997).
135. Bernier J, Brousseau P, Krzystyniak K, Tryphonas H, Fournier M. Immunotoxicity of heavy metals in relation to Great Lakes. Environ Health Perspect 103(suppl 9):23–34 (1995).
136. Weiner JA, Nylander M. Aspects on health risks of mercury from dental amalgams. In: Toxicology of Metals (Chang LW, ed). Boca Raton, FL:CRC Lewis Publishers, 1996;469–486.
137. The Safety of Dental Amalgam: a State of the Art Review. Montreal:Conseil d'Évaluation des Technologies de la Santé de Quebec, 1997.
138. Fung MC, Bowen DL. Silver products for medical indications: risk-benefit assessment. J Toxicol Clin Toxicol 34:119–126 (1996).
139. Sharma RP, Dugyala RR. Effects of metals on cell-mediated immunity and biological response modulators. In: Toxicology of Metals (Chang LW, ed). Boca Raton, FL:CRC Lewis Publishers, 1996;785–796.
140. Exon JH, South EH, Hendrix K. Effects of metals on the humoral immune response. In: Toxicology of Metals (Chang LW, ed). Boca Raton, FL:CRC Lewis Publishers, 1996;797–810.
141. Zelikoff JT, Smialowicz RJ. Metal-induced alterations in innate immunity. In: Toxicology of Metals (Chang LW, ed). Boca Raton, FL:CRC Lewis Publishers, 1996;811–826.
142. Shenker BJ, Datar S, Mansfield K, Shapiro IM. Induction of apoptosis in human T-cells by organomercuric compounds: a flow cytometric analysis. Toxicol Appl Pharmacol 143:397–406 (1997).
143. Prigent P, Poncet P, Aten J, Blanpied C, Chand A, Février M, Druet P, Hirsch F. Mercuric chloride-induced programmed cell death of a murine hybridoma. II: Opposite effect of interleukin-2 and interleukin-4. Cell Immunol 161:107–111 (1995).
144. van der Meide PH, de Labie MCDC, Botman CAD, van Bennekom WP, Olsson T, Aten J, Weening JJ. Mercuric chloride down-regulates T cell interferon-γ production in Brown Norway but not in Lewis rats; role of glutathione. Eur J Immunol 23:675–681 (1993).
145. van der Meide PH, de Labie MCDC, Botman CAD, Aten J, Weening JJ. Nitric oxide suppresses IFN-γ production in the spleen of mercuric chloride-exposed Brown Norway rats. Cell Immunol 161:195–206 (1995).
146. Reardon CL, Lucas DO. Zn^{++} and Hg^{++} mediated induction of mitogenesis, cell-mediated cytotoxicity, and interferon production in murine lymphocytes. In: Intercellular Communication in Leukocyte Function (Parker JW, O'Brien RL, eds). New York:John Wiley & Sons, 1983;449–452.
147. Reardon CL, Lucas DO. Heavy metal mitogenesis: Zn^{++} and Hg^{++} induce cellular cytotoxicity and interferon production in murine T lymphocytes. Immunobiology 175:455 (1987).
148. Ochel M, Vohr HW, Pfeiffer C, Gleichmann E. IL-4 is required for the IgE and IgG1 increase and IgG1 autoantibody formation in mice treated with mercuric chloride. J Immunol 146:3006–3011 (1991).
149. Prouvost-Danon A, Abadie A, Sapin C, Bazin H, Druet P. Induction of IgE synthesis and potentiation of anti-ovalbumin IgE antibody response by $HgCl_2$ in the rat. J Immunol 126:699–702 (1981).
150. Kimata H, Shinomiya K, Mikawa H. Selective enhancement of human IgE production *in vitro* by synergy of pokeweed mitogen and mercuric chloride. Clin Exp Immunol 53:183–191 (1983).
151. Sapin C, Hirsch F, Delaporte JP, Bazin H, Druet P. Polyclonal IgE increase after $HgCl_2$ injections in BN and LEW rats: a genetic analysis. Immunogenetics 20:227–236 (1984).
152. Daum JR, Shepherd DM, Noelle RJ. Immunotoxicology of cadmium and mercury on B-lymphocytes. I: Effects on lymphocyte function. Int J Immunopharmacol 15:383–394 (1993).
153. Al-Balaghi S, Möller E, Möller G, Abedi-Valugerdi M. Mercury induces polyclonal B-cell activation, autoantibody production and renal immune complex deposits in young (NZB×NZW)F1 hybrids. Eur J Immunol 26:1519–1526 (1996).
154. Johansson U, Hansson-Georgiadis H, Hultman P. The genotype determines the B cell response in mercury-treated mice. Int Arch Allergy Immunol 116:295–305 (1998).
155. Contrino J, Kosuda LL, Marucha P, Kreutzer DL, Bigazzi PE. The *in vitro* effects of mercury on peritoneal leukocytes (PMN and macrophages) from inbred Brown Norway and Lewis rats. Int J Immunopharmacol 14:1051–1059 (1992).
156. Zdolsek JM, Soder O, Hultman P. Mercury induces *in vivo* and *in vitro* secretion of interleukin-1 in mice. Immunopharmacology 28:201–208 (1994).
157. Contrino J, Marucha P, Ribaudo R, Ference R, Bigazzi PE, Kreutzer DL. Effects of mercury on human polymorphonuclear leukocyte function *in vitro*. Am J Pathol 132:110–118 (1988).
158. Baginski B. Effect of mercuric chloride on microbicidal activities of human polymorphonuclear leukocytes. Toxicology 50:247–256 (1988).
159. Oliveira DBG, Wolfreys K, Coleman JW. Compounds that induce Th2-driven autoimmunity in Brown Norway rats sensitize their mast cells *in vitro*. Hum Exp Toxicol 13:615 (1994).
160. Warbrick EV, Thomas AL, Coleman JW. The effects of mercuric chloride on growth, cytokine and MHC class II gene expression in a human leukemic mast cell line. Toxicology 104:179–186 (1995).
161. Ilback NG, Sundberg J, Oskarsson A. Methyl mercury exposure via placenta and milk impairs natural killer (NK) cell function in newborn rats. Toxicol Lett 58:149–158 (1991).
162. Wild LG, Ortega HG, Lopez M, Salvaggio JE. Immune system alteration in the rat after indirect exposure to methyl mercury chloride or methyl mercury sulfide. Environ Res 74:34–42 (1997).
163. Shenker BJ, Berthold P, Rooney C, Vitale L, DeBolt K, Shapiro IM. Immunotoxic effects of mercuric compounds on human lymphocytes and monocytes. III: Alterations in B-cell function and viability. Immunopharmacol Immunotoxicol 15:87–112 (1993).
164. Mathieson PW, Gillespie KM. Cloning of a partial cDNA for rat interleukin-12 (IL-12) and analysis of IL-12 expression *in vivo*. Scand J Immunol 44:11–14 (1996).
165. Malamud D, Dietrich SA, Shapiro IM. Low levels of mercury inhibit the respiratory burst in human polymorphonuclear leukocytes. Biochem Biophys Res Commun 128:1145–1151 (1985).
166. Obel N, Hansen B, Christensen MM, Nielsen SL, Rungby J. Methyl mercury, mercuric chloride, and silver lactate decrease superoxide anion formation and chemotaxis in human polymorphonuclear leucocytes. Hum Exp Toxicol 12:361–364 (1993).
167. Tubbs RR, Gephardt GN, McMahon JT, Phol MC, Vidt DG, Barenberg SA, Valenzuela R. Membranous glomerulonephritis associated with industrial mercury exposure. Am J Clin Pathol 77:409–413 (1982).
168. Majno G, Joris I. Cells, Tissues, and Disease: Principles of General Pathology. Cambridge, MA:Blackwell Science, 1996.
169. Drachman DB. Myasthenia Gravis. In: The Autoimmune Diseases (Rose NR, Mackay I, eds). San Diego:Academic Press, 1998;637–662.
170. Weetman AP. Autoimmune thyroid disease. In: The Autoimmune Diseases (Rose NR, Mackay I, eds). San Diego:Academic Press, 1998;405–430.
171. Langworth S, Elinder CG, Sundquist KG, Vesterberg O. Renal and immunological effects of occupational exposure to inorganic mercury. Br J Ind Med 49:394–401 (1992).
172. Langworth S, Elinder CG, Sundquist KG. Minor effects of low exposure to inorganic mercury on the human immune system. Scand J Work Environ Health 19:405–413 (1993).
173. Barregård L, Enestrom S, Ljunghusen O, Wieslander J, Hultman P. A study of autoantibodies and circulating immune complexes in mercury-exposed chloralkali workers. Int Arch Occup Environ Health 70:101–106 (1997).
174. Hultman P, Lindh U, Hörsted-Bindslev P. Activation of the immune system and systemic immune-complex deposits in Brown Norway rats with dental amalgam restorations. J Dent Res 77:1415–1425 (1998).
175. Roman-Franco AA, Turiello M, Albini B, Ossi E, Milgrom F, Andres GA. Anti-basement membrane antibodies and antigen-antibody complexes in rabbits injected with mercuric chloride. Clin Immunol Immunopathol 9:464–481 (1978).
176. Goter Robinson CJ, Abraham AA, Balasz T. Induction of antinuclear antibodies by mercuric chloride in mice. Clin Exp Immunol 58:300–306 (1984).
177. Hultman P, Enestrom S. The induction of immune complex deposits in mice by peroral and parenteral administration of mercuric-chloride-strain dependent susceptibility. Clin Exp Immunol 67:283–292 (1987).
178. Hultman P, Enestrom S. Mercury induced antinuclear antibodies in mice: characterization and correlation with renal immune complex deposits. Clin Exp Immunol 71:269–274 (1988).
179. Hultman P, Enestrom S, Pollard KM, Tan EM. Anti-fibrillarin autoantibodies in mercury-treated mice. Clin Exp Immunol 78:470–477 (1989).
180. Reuter R, Tessars G, Vohr H-W, Gleichmann E, Lührmann R. Mercuric chloride induces autoantibodies to small nuclear ribonucleoprotein in susceptible mice. Proc Natl Acad Sci USA 86:237–241 (1989).
181. Goter-Robinson CJ, White HJ, Rose NR. Murine strain differences in response to mercuric chloride: antinucleolar antibodies production does not correlate with renal immune complex deposition. Clin Immunol Immunopathol 83:127–138 (1997).
182. Hultman P, Enestrom S. Mercury induced B-cell activation and antinuclear antibodies in mice. J Clin Lab Immunol 28:143–150 (1989).
183. Hultman P, Enestrom S. Dose-response studies in murine mercury-induced autoimmunity and immune-complex disease. Toxicol Appl Pharmacol 113:199–208 (1992).
184. Saegusa J, Yamamoto S, Iwai H, Ueda K. Antinucleolar autoantibody induced in mice by mercuric chloride. Ind Health 28:21–30 (1990).
185. Monestier M, Losman MJ, Novick KE, Aris JP. Molecular analysis of mercury-induced antinucleolar antibodies in $H\text{-}2^s$ mice. J Immunol 152:667–675 (1994).
186. Reichlin M. Systemic lupus erythematosus. In: The Autoimmune Diseases (Rose NR, Mackay I, eds). San Diego:Academic Press, 1998;283–298.
187. Hultman P, Bell LJ, Enestrom S, Pollard KM. Murine susceptibility to mercury. I: Autoantibody profiles and systemic immune deposits in inbred, congenic and intra-H-2 recombinant strains. Clin Immunol Immunopathol 65:98–109 (1992).
188. Hultman P, Turley SJ, Enestrom S, Lindh U, Pollard KM. Murine genotype influences the specificity, magnitude and persistence of murine mercury-induced autoimmunity. J Autoimmun 9:139–149 (1996).
189. Bariety J, Druet P, Laliberte F, Sapin C. Glomerulonephritis with γ- and β1c-globulin deposits induced in rats by mercuric chloride. Am J Pathol 65:293–300 (1971).
190. Sapin C, Druet E, Druet P. Induction of anti-glomerular base-

ment membrane antibodies in the Brown-Norway rat by mercuric chloride. Clin Exp Immunol 28:173–179 (1977).
191. Druet E, Sapin C, Günther E, Feingold N, Druet P. Mercuric chloride-induced anti-glomerular basement membrane antibodies in the rat. Genetic control. Eur J Immunol 7:348–351 (1977).
192. Henry GA, Jarnot BM, Steinhoff MM, Bigazzi PE. Mercury-induced renal autoimmunity in the MAXX rat. Clin Immunol Immunopathol 49:187–203 (1988).
193. Aten J, Bosman CB, Rozing J, Stijnen T, Hoedemaeker PJ, Weening JJ. Mercuric chloride-induced autoimmunity in the Brown Norway rat. Am J Pathol 133:127–138 (1988).
194. Aten J, Veninga A, Bruijn JA, Prins FA, de Heer E, Weening JJ. Antigenic specificities of glomerular-bound autoantibodies in membranous glomerulopathy induced by mercuric chloride. Clin Immunol Immunopathol 63:89–102 (1992).
195. Weening JJ, Fleuren GJ, Hoedemaeker PJ. Demonstration of antinuclear antibodies in mercuric chloride-induced glomerulopathy in the rat. Lab Invest 39:405–411 (1978).
196. Weening JJ, Grond J, Van der Top D, Hoedemaeker PJ. Identification of the nuclear antigen involved in mercury-induced glomerulopathy in the rat. Invest Cell Pathol 3:129–134 (1980).
197. Kosuda LL, Greiner DL, Bigazzi PE. Effects of $HgCl_2$ on the expression of autoimmune responses and disease in diabetes-prone (DP) BB rats. Autoimmunity 26:173–187 (1997).
198. Pelletier L, Galceran M, Pasquier R, Ronco P, Verroust P, Bariety J, Druet P. Down modulation of Heymann's nephritis by mercuric chloride. Kidney Int 32:227–232 (1987).
199. Pelletier L, Pasquier R, Rossert J, Druet P. $HgCl_2$ induces non-specific immunosuppression in Lewis rats. Eur J Immunol 17:49–54 (1987).
200. Pelletier L, Rossert J, Pasquier R, Villarroya H, Belair M-F, Vial M-C, Oriol R, Druet P. Effect of $HgCl_2$ on experimental allergic encephalomyelitis in Lewis rats. $HgCl_2$-induced down-modulation of the disease. Eur J Immunol 18:243–247 (1988).
201. Aten J, Veninga A, Coers W, Sonnenberg A, Timpl R, Claessen N, van Eendenburg JDH, de Heer E, Weening JJ. Autoantibodies to the laminin P1 fragment in $HgCl_2$-induced membranous glomerulopathy. Am J Pathol 146:1467–1480 (1995).
202. Kosuda LL, Whalen B, Greiner DL, Bigazzi PE. Mercury-induced autoimmunity in Brown Norway rats: kinetics of changes in RT6+ T lymphocytes correlated with IgG isotypes of circulating autoantibodies to laminin 1. Toxicology 125:215–231 (1998).
203. Capron M, Ayed K, Druet E, Sapin C, Mandet C, Druet P, Girard JF. Complement studies in BN rats with mercuric chloride-induced immune glomerulonephritis. Ann Immunol (Inst Pasteur) 131D:43–55 (1980).
204. Aten J, Veninga A, De Heer E, Rozing J, Nieuwenhuis P, Hoedemaeker PJ, Weening JJ. Susceptibility to the induction of either autoimmunity or immunosuppression by mercuric chloride is related to the major histocompatibility complex class II haplotype. Eur J Immunol 21:611–616 (1991).
205. Bernaudin JF, Druet E, Belair MF, Pinchon MC, Sapin C, Druet P. Extrarenal immune complex type deposits induced by mercuric chloride in the Brown Norway rat. Clin Exp Immunol 38:265–273 (1979).
206. Andres P. IgA-IgG disease in the intestine of Brown-Norway rats ingesting mercuric chloride. Clin Immunol Immunopathol 30:488–494 (1984).
207. Hinglais N, Druet P, Grossetete J, Sapin C, Bariety J. Ultrastructural study of nephritis induced in Brown Norway rats by mercuric chloride. Lab Invest 41:150–159 (1979).
208. Hirszel P, Michaelson JH, Dodge K, Yamase H, Bigazzi PE. Mercury-induced autoimmune glomerulonephritis in inbred rats. II: Immunohistopathology, histopathology and effects of prostaglandin administration. Surv Synth Pathol Res 4:412–422 (1985).
209. Kosuda LL, Hannigan MO, Bigazzi PE, Leif JH, Greiner DL. Thymus atrophy and changes in thymocyte subpopulations of BN rats with mercury-induced renal autoimmune disease. Autoimmunity 23:77–89 (1996).
210. Kosuda LL, Wayne A, Nahounou M, Greiner DL, Bigazzi PE. Reduction of the RT6.2+ subset of T lymphocytes in Brown Norway rats with mercury-induced renal autoimmunity. Cell Immunol 135:154–167 (1991).
211. Greiner DL, Mordes JP, Angelillo M, Handler ES, Mojcik CF, Nakamura N, Rossini A. Role of regulatory $RT6^+$ T cells in the pathogenesis of diabetes mellitus in BB/Wor rats. In: Frontiers in Diabetes Research: Lessons from Animal Diabetes (Renold A, Shafrir E, eds). London:John Libby & Co., 1988;18–27.
212. Greiner D, Malkani S, Kanaitsuka T, Bortell R, Doukas J, Rigby M, Whalen B, Stevens L, Moss J, Mordes J, et al. The T cell marker RT6 in a rat model of autoimmune diabetes. In: ADP-Ribosylation in Animal Tissues. Structure, Function, and Biology of Mono (ADP-ribosyl) Transferases and Related Enzymes (Haag FA, Koch-Nolte F, eds). New York:Plenum Press, 1997;209–216.
213. Fowell D, Powrie F, Saoudi A, Seddon B, Heath V, Mason D. The role of subsets of $CD4^+$ T cells in autoimmunity. Ciba Found Symp 195:173–188 (1995).
214. Mason D, Powrie F. Control of immune pathology by regulatory T cells. Curr Opinion Immunol 10:649–655 (1998).
215. Qasim FJ, Thiru S, Mathieson PW, Oliveira DBG. The time course and characterization of mercuric chloride-induced immunopathology in the Brown Norway rat. J Autoimmun 8:193–208 (1995).
216. Esnault VLM, Mathieson PW, Thiru S, Oliveira DBG, Lockwood CM. Autoantibodies to myeloperoxidase in Brown Norway rats treated with mercuric chloride. Lab Invest 67:114–120 (1992).
217. Mathieson PW. Mercuric chloride-induced autoimmunity. Autoimmunity 13:243–247 (1992).
218. Mathieson PW, Thiru S, Oliveira DBG. Mercuric chloride-treated Brown Norway rats develop widespread tissue injury including necrotizing vasculitis. Lab Invest 67:121–129 (1992).
219. Qasim FJ, Mathieson PW, Thiru S, Oliveira DBG, Lockwood CM. Further characterization of an animal model of systemic vasculitis. In: ANCA-Associated Vasculitides: Immunological and Clinical Aspects (Gross WL, ed). New York:Plenum Press, 1993;133–137.
220. Peszkowski MJ, Warfvinge G, Larsson Å. $HgCl_2$-induced glandular pathosis in the Brown Norway rat. Clin Immunol Immunopathol 69:272–277 (1993).
221. Warfvinge G, Peszkowski MJ, Hultman P, Larsson Å. Oral, perioral and systemic pathosis in $HgCl_2$-induced autoimmunity in the BN rat. Eur J Oral Sci 105:153–161 (1997).
222. Druet E, Sapin C, Fournie G, Mandet C, Gunther E, Druet P. Genetic control of susceptibility to mercury-induced immune nephritis in various strains of rat. Clin Immunol Immunopathol 25:203–212 (1982).
223. Kosuda LL, Greiner DL, Bigazzi PE. Mercury-induced renal autoimmunity in BN→LEW.1N chimeric rats. Cell Immunol 155:77–94 (1994).
224. Bridoux F, Badou A, Saoudi A, Bernard I, Druet E, Pasquier R, Druet P, Pelletier L. Transforming growth factor beta (TGF-beta)-dependent inhibition of T helper cell 2 (Th2)-induced autoimmunity by self-major histocompatibility complex (MHC) class II-specific regulatory $CD4(+)$ T cell lines. J Exp Med 185:1769–1775 (1997).
225. Romagnoli P, Spinas GA, Sinigaglia F. Gold-specific T cells in rheumatoid arthritis patients treated with gold. J Clin Invest 89:254–258 (1992).
226. Pelletier L, Pasquier R, Hirsch F, Sapin C, Druet P. *In vivo* self-reactivity of mononuclear cells to T cells and macrophages exposed to $HgCl_2$. Eur J Immunol 15:460–465 (1985).
227. Mongey A-B, Hess EV. Drug and environmental lupus: clinical manifestations and differences. In: Systemic Lupus Erythematosus (Lahita RG, ed). San Diego:Academic Press, 1999;929–943.
228. Yung RL, Richardson BC. Pathophysiology of drug-induced lupus. In: Systemic Lupus Erythematosus (Lahita RG, ed). San Diego:Academic Press, 1999;909–928.
229. Druet E, Guery J-C, Ayed K, Guilbert B, Avrameas S, Druet P. Characteristics of polyreactive and monospecific IgG anti-laminin autoantibodies in the rat mercury model. Immunology 83:489–494 (1994).
230. Khalil M, Spatz L, Diamond B. Anti-DNA antibodies. In: Systemic Lupus Erythematosus (Lahita RG, ed). San Diego:Academic Press, 1999;197–217.
231. Reichlin M. Antibodies to cytoplasmic antigens. In: Systemic Lupus Erythematosus (Lahita RG, ed). San Diego:Academic Press, 1999;219–226.
232. Fritzler MJ, Andrade L. Antibodies to nonhistone antigens in Systemic Lupus Erythematosus. In: Systemic Lupus Erythematosus (Lahita RG, ed). San Diego:Academic Press, 1999;247–267.
233. Satoh M, Hamilton KJ, Ajmani AK, Dong X, Wang J, Kanwar YS, Reeves WH. Autoantibodies to ribosomal P antigens with immune complex glomerulonephritis in SJL mice treated with pristane. J Immunol 157:3200–3206 (1996).
234. Lahita RG. The clinical presentations of Systemic lupus erythematosus. In: Systemic Lupus Erythematosus (Lahita RG, ed). San Diego:Academic Press, 1999, 325–336.
235. Balow JE, Boumpas DT, Austin HAI. Systemic lupus erythematosus and the kidney. In: Systemic Lupus Erythematosus (Lahita RG, ed). San Diego:Academic Press, 1999;657–685.
236. Black C, Denton CP. Scleroderma—systemic sclerosis. In: Oxford Textbook of Clinical Nephrology (Davison AM, Cameron JS, Grünfeld J-P, Kerr DNS, Ritz E, Winearls CG, eds). Oxford, UK:Oxford University Press, 1998;961–973.
237. Pollard KM, Lee DK, Casiano CA, Blüthner M, Johnston MM, Tan EM. The autoimmunity-inducing xenobiotic mercury interacts with the autoantigen fibrillarin and modifies its molecular and antigenic properties. J Immunol 158:3521–3528 (1997).
238. Goldman M, Druet P, Gleichmann E. TH2 cells in systemic autoimmunity: insights from allogeneic diseases and chemically-induced autoimmunity. Immunol Today 12:223–227 (1991).
239. Kono DH, Balomenos D, Pearson DL, Park MS, Hildebrandt B, Hultman P, Pollard KM. The prototypic Th2 autoimmunity induced by mercury is dependent on IFN-γ and not Th1/Th2 imbalance. J Immunol 161:234–240 (1998).